A. M. A.
ARCHIVES OF
INTERNAL MEDICINE

EDITORIAL BOARD

PAUL S. RHOADS, Chief Editor, Chicago

ARTHUR BLOOMFIELD, San Francisco
REGINALD FITZ, Boston
GEORGE E. BURCH, New Orleans
LOUIS LEITER, New York
HUGH R. BUTT, Rochester, Minn.
RUSSELL M. WILDER, Washington, D. C.
BRUCE K. WISEMAN, Columbus, Ohio

FEBRUARY 1953

VOLUME 91 NUMBER 2

Published Monthly by

AMERICAN MEDICAL ASSOCIATION

535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Jan. 23, 1909, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $10.00

TABLE OF CONTENTS FIRST PAGE

ganglionic block in hypertension

to reduce blood pressure and relieve symptoms—a new, potent oral hypotensive

Extensive clinical use has demonstrated Methium's ability to

1. reduce blood pressure to more normal levels
2. relieve hypertensive symptoms
3. provide symptomatic relief in some cases even where pressure cannot be lowered.

An autonomic ganglionic blocking agent, Methium *(hexamethonium chloride)* inhibits nerve impulses that produce vasoconstriction—thereby causing blood pressure to fall.

In successfully treated patients, receding pressure is accompanied by relief of headache, dizziness, palpitation and fatigue. In other cases, where blood pressure does not respond to therapy, symptomatic improvement may nonetheless be noted.

Methium is a potent drug and should be used with great caution when complications exist — impaired renal function, coronary artery disease and existing or threatened cerebral vascular accidents. Complete instructions for prescribing Methium are available on request and should be consulted before using the drug.

Methium is supplied in both 125 mg. and 250 mg. scored tablets in bottles of 100 and 500.

Methium® CHLORIDE

(BRAND OF HEXAMETHONIUM CHLORIDE)

WARNER-CHILCOTT *Laboratories*, NEW YORK

CONTENTS

Original Articles

Antibiotic Resistance of Pathogenic Staphylococci PAGE

Maxwell Finland, M.D., and Thomas H. Haight, M.D., with the Technical Assistance of Clare Wilcox and Marilyn K. Broderick, Boston 143

Liver Coma, with Particular Reference to Management

Michael M. Karl, M.D; Roy A. Howell, M.D.; James H. Hutchinson, M.D., and Frank J. Catanzaro, M.D., St. Louis 159

Clinical and Laboratory Study of Thirty-One Patients with Hemorrhagic Fever

Captain Giulio J. Barbero; Captain Sidney Katz; Lieutenant Henry Kraus, and Colonel Charles L. Leedham, Medical Corps, United States Army 177

Lack of Interference of Aureomycin with Penicillin in Treatment of Pneumococcic Pneumonia

James J. Ahern, M.D., and William M. M. Kirby, M.D., Seattle 197

Oxytetracycline-Streptomycin Therapy in Brucellosis Due to Brucella Melitensis

Gordon B. Magill, M.D., and John H. Killough, Ph.D., M.D., Cairo, Egypt 204

Involvement of Bone Marrow in Diffuse Pulmonary Disease

Austin S. Weisberger, M.D., and Robert M. Dumm, M.D., Cleveland 212

Secondary Tumors of Heart and Pericardium

Major James F. DeLoach and Major James W. Haynes, Medical Corps, United States Air Force 224

Cardiovascular Lesions Following Bilateral Nephrectomy of Dog

E. E. Muirhead, M.D.; J. A. Stirman, M.D.; Frances Jones, M.S.; Warren Lesch, M.A.; Marjorie Burns, B.S., and M. J. Fogelman, M.D., Dallas, Texas 250

Case Reports

Pleuropulmonary Tularemia Complicated by Peripheral Neuritis

Mortimer Raphael, M.D., and Augustus E. Anderson, M.D., New Orleans 278

Regular Departments

Books 281

THE A. M. A. ARCHIVES OF INTERNAL MEDICINE is published by the American Medical Association for the advancement of scientific medicine in the United States and for the reporting of research and observation in the domain of internal medicine.

Manuscripts for publication, books for review and correspondence relating to the editorial management should be sent to the Chief Editor, Dr. Paul S. Rhoads, 535 North Dearborn Street, Chicago 10. Communications regarding subscriptions, reprints, etc., should be addressed, A. M. A. ARCHIVES OF INTERNAL MEDICINE, American Medical Association, 535 North Dearborn Street, Chicago 10.

Articles are accepted for publication on condition that they are contributed solely to the A. M. A. ARCHIVES OF INTERNAL MEDICINE. Manuscripts must be typewritten, preferably double spaced, and the original copy should be submitted. Zinc etchings and halftones will be supplied by the Association when the original illustrations warrant reproduction and when their number is not considered excessive.

Footnotes and bibliographies (the latter are used only in exhaustive reviews of the literature) should conform to the style of the *Quarterly Cumulative Index Medicus*. This requires, in the order given: name of author, title of article and name of periodical, with volume, page, month—day of month if the journal appears weekly—and year.

Matter appearing in the A. M. A. ARCHIVES OF INTERNAL MEDICINE is covered by copyright, but as a rule no objection will be made to its reproduction in a reputable medical journal if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the A. M. A. ARCHIVES OF INTERNAL MEDICINE or in any of the other publications issued by the Association will not be permitted.

The A. M. A. ARCHIVES OF INTERNAL MEDICINE is published monthly. The annual subscription price (for two volumes) is as follows: domestic, $10.00; Canadian, $10.40; foreign, $11.00, including postage. Current single copies are $1.00, postpaid.

Checks, money orders and drafts should be made payable to the American Medical Association.

OTHER PERIODICAL PUBLICATIONS
of the American Medical Association

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION—Weekly. Covers all the medical sciences and matters of general medical interest. Illustrated. Annual subscription price (three volumes): domestic, $15.00; Canadian, $16.50; foreign, $19.00. Single copies, 45 cents.

A. M. A. ARCHIVES OF NEUROLOGY AND PSYCHIATRY—Monthly. A medium for the presentation of original articles on nervous and mental diseases, with abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.50. Single copies, $1.25.

A. M. A. ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY—Monthly. Devoted to advancing the knowledge of and progress in cutaneous diseases and syphilis. Publishes original contributions on these two subjects, transactions of the important dermatological societies, book reviews, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.50. Single copies, $1.25.

A. M. A. AMERICAN JOURNAL OF DISEASES OF CHILDREN—Monthly. Presents pediatrics as a medical science and as a social problem. Includes carefully prepared reviews, based on recent pediatric literature, abstracts from foreign and domestic literature, book reviews, transactions of special societes, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.50. Single copies, $1.25.

A. M A. ARCHIVES OF SURGERY—Monthly. Devoted largely to the investigative and clinical phases of surgery, with monthly reviews on orthopedic and urologic surgery. Well Illustrated. Annual subscription price (two volumes): domestic, $14.00; Canadian, $14.40; foreign, $15.50. Single copies, $1.25, except special numbers.

A. M. A. ARCHIVES OF OPHTHALMOLOGY—Monthly. Includes original articles on diseases of the eye, annual reviews of special subjects, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.00. Single copies, $1.25.

A. M. A. ARCHIVES OF OTOLARYNGOLOGY—Monthly. A medium for the presentation of original articles on diseases of the ear, nose and throat, with abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.00. Single copies, $1.25.

A. M. A. ARCHIVES OF PATHOLOGY—Monthly. A periodical devoted to the publication of original articles and general reviews in the field of pathology. Illustrated. Annual subscription price (two volumes): domestic, $8.00; Canadian, $8.40; foreign, $9.00. Single copies, $1.00, except special issues.

A. M. A. ARCHIVES OF INDUSTRIAL HYGIENE AND OCCUPATIONAL MEDICINE—Monthly. Devoted to the advancement of knowledge of the diseases of industry and to the publication of scientific investigation in this field. Illustrated. Annual subscription price (two volumes): domestic, $8.00; Canadian, $8.40; foreign, $9.00, including postage. Single copies, $1.00.

QUARTERLY CUMULATIVE INDEX MEDICUS—A complete subject and author index to the worth while current medical literature of the world. Issued twice a year. Volumes bound for permanent reference. Subscription price, calendar year: domestic, $20.00; Canadian, $22.00; foreign, $22.00.

AMERICAN MEDICAL ASSOCIATION

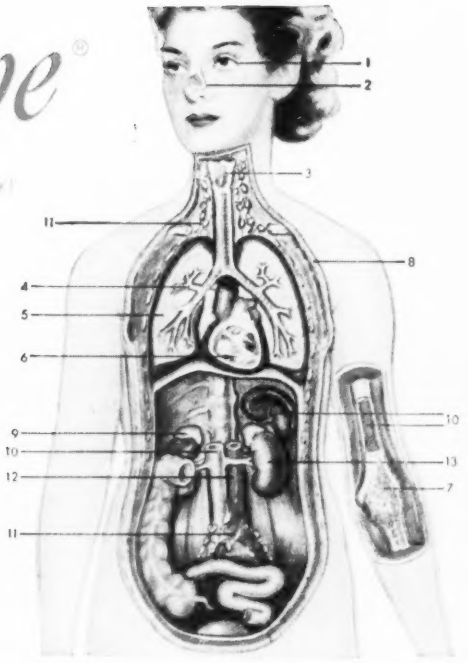
535 North Dearborn Street **CHICAGO 10**

Cortone®

ACETATE

(CORTISONE ACETATE, MERCK)

The many indications for CORTONE *highlight its therapeutic importance in everyday practice*



Primary Site of Pathology and Indications

1. EYE—Inflammatory eye disease. **2. NOSE**—Intractable hay fever. **3. LARYNX**—Laryngeal edema (allergic). **4. BRONCHI**—Intractable bronchial asthma. **5. LUNG**—Sarcoidosis. **6. HEART**—Acute rheumatic fever with carditis. **7. BONES AND JOINTS**—Rheumatoid arthritis; Rheumatoid spondylitis; Acute gouty arthritis; Still's Disease; Psoriatic arthritis. **8. SKIN AND CONNECTIVE TISSUE**—Pemphigus; Exfoliative dermatitis; Atopic dermatitis; Disseminated lupus erythematosus; Scleroderma (early); Dermatomyositis; Poison Ivy. **9. ADRENAL GLAND**—Congenital adrenal hyperplasia; Addison's Disease; Adrenalectomy for hypertension, Cushing's Syndrome, and neoplastic diseases. **10. BLOOD, BONE MARROW, AND SPLEEN**—Allergic purpura; Acute leukemia† (lymphocytic or granulocytic); Chronic lymphatic leukemia.† **11. LYMPH NODES**—Lymphosarcoma†; Hodgkin's Disease†. **12. ARTERIES AND CONNECTIVE TISSUE**—Periarteritis nodosa (early). **13. KIDNEY**—Nephrotic Syndrome, without uremia (to induce withdrawal diuresis). **14. VARIOUS TISSUES**—Sarcoidosis; Angioneurotic edema; Drug sensitization; Serum sickness; Waterhouse-Friderichsen Syndrome.

†Transient beneficial effects.

CORTONE is the registered trade-mark of Merck & Co., Inc. for its brand of cortisone.

MERCK & CO., INC.

Manufacturing Chemists

RAHWAY, NEW JERSEY

Only the WHOLE Fruit

CAN GIVE YOU ALL ITS NUTRITIONAL BENEFITS...

As shown by the comparative tables below, only the whole orange can provide all of the valuable nutritional benefits of the fruit.

While orange juice is a popular and pleasant way to provide the daily quota of vitamin C, the fact is that the whole fruit is considerably richer in vitamin C and other nutrients as well as in the protopectins. These substances, the protopectins, are found principally in the albedo, the membranes enclosing the juice sacs and segments, and the fibrovascular bundles.

Only when oranges are eaten whole can *all* the benefits of the fruit be realized, especially the desirable effects of the protopectins which, through their colloidal, chemical, and antibacterial properties, help to maintain a desirable intestinal environment, promote better absorption of vitamins and minerals, and effect more normal evacuation.

Approximate Typical Analyses of Edible Portion and Strained Juice of California Oranges.
Amounts shown are per 100 Gm. of fresh weight.

Constituents	Fresh Fruit, peeled	Strained Juice	Constituents	Fresh Fruit, peeled	Strained Juice
Calories	46	46	Inositol	400.0 mg.	200.0 mg.
Protein (including free amino acids*)[1,4]	1.0 Gm.	0.9 Gm.	Biotin	0.004 mg.	0.002 mg.
Fat	0.3 Gm.	0.2 Gm.	Folic acid	0.004 mg.	0.002 mg.
Dextrose and Levulose	4.0 Gm.	4.6 Gm.	Ascorbic acid (vitamin C)	60.0 mg.	57.0 mg.
Sucrose	4.0 Gm.	4.6 Gm.	Flavonoids (vitamin "P")[3]	1.0 Gm.	0.1 Gm.
Protopectins and Pectin	1.0 Gm.[3]	0.1 Gm.	Minerals (total ash)	0.5 Gm.	0.4 Gm.
Citric acid	1.0 Gm.	1.0 Gm.	Calcium	50.0 mg.	11.6 mg.
Malic acid	0.1 Gm.	0.1 Gm.	Phosphorus	30.0 mg.	20.0 mg.
Carotenes (pro-vitamin A)	1.0 mg.	0.16 mg.	Iron	1.0 mg.	0.25 mg.
Thiamine (vitamin B_1)	0.2 mg.	0.086 mg.	Sodium	9.0 mg.	6.0 mg.
Riboflavin	0.1 mg.	0.032 mg.	Potassium	150.0 mg.	170.0 mg.
Niacin	0.5 mg.	0.24 mg.	Magnesium	10.0 mg.	13.0 mg.
Pantothenic acid	0.5 mg.	0.21 mg.	Sulfur	10.0 mg.	8.0 mg.
Pyridoxine	0.2 mg.	0.08 mg.	Chlorine	6.0 mg.	6.0 mg.
			Alkalinity of ash, expressed as K_2CO_3	0.3 Gm.	0.3 Gm.

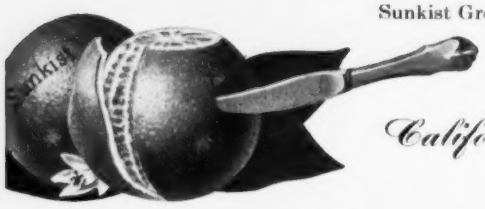
* Free amino acids include alanine, arginine, asparagine, cysteine, serine, proline, and glutamic, aspartic and gamma-aminobutyric acids. Glutathione is also present.

1. Underwood, J. C., and Rockland, L. B.: Food Research, in press.
2. Miner Laboratories, Chicago, Illinois. (1952)
3. Davis, W. B.: Determination of Flavanones in Citrus Fruits, Anal. Chem. 19:476 (July) 1947.
4. Underwood, J. C., and Rockland, L. B.: Arch. Biochem., in press.

All others from figures taken from the literature and data compiled by Research Department, Sunkist Growers. From known tissue distribution figures, appropriate adjustments have been made to reflect the composition of the entire edible portion in those cases where the original data referred to screened juice.

California navel oranges, available all winter, are the world's finest eating oranges—no seeds, rich in flavor and vitamins. Easiest to peel, slice and section.

Sunkist Growers · Los Angeles, California



Sunkist®

California-Arizona Oranges

Upjohn

long-acting
androgen:

Depo-Testosterone

Trademark Reg. U.S. Pat. Off.

CYCLOPENTYLPROPIONATE

Each cc. contains:

Testosterone Cyclopentylpropionate .....50 mg. or 100 mg.
Chlorobutanol ..... 5 mg.
Cottonseed Oil .....q.s.

50 mg. per cc. available in 10 cc. vials

100 mg. per cc. available in 1 cc. and 10 cc. vials

The Upjohn Company, Kalamazoo, Michigan

to prevent attacks in angina pectoris

Effective in 4 out of 5 cases — Fewer anginal attacks were suffered by 78.4%[1] and 80%[2] of patients for whom Peritrate was prescribed on a continuing daily schedule. Taken regularly as a prophylactic measure (rather than when attack is present or imminent), Peritrate will often help to

1. reduce the number of attacks
2. reduce the severity of those attacks that are not prevented
3. reduce nitroglycerin dependence
4. increase exercise tolerance.

New, long-lasting oral vasodilator — Unlike older, shorter-acting nitrates, Peritrate is slowly absorbed and long-lasting, each dose providing 4 to 5 hours protection against attacks. It is virtually nontoxic. Mild, transitory side effects occur rarely and are easily controlled. Tolerance has not developed in patients studied.

Dosage: Usually 1 tablet 3 or 4 times daily. Available in 10 mg. tablets in bottles of 100 and 500. Literature and samples on request.

1. Humphreys, P., et al.: Angiology 3:1 (Feb.) 1952.
2. Plotz, M.: N.Y. State J. Med. 52:2012 (Aug. 15) 1952.

Peritrate® TETRANITRATE

(BRAND OF PENTAERYTHRITOL TETRANITRATE)

WARNER-CHILCOTT
Laboratories, NEW YORK

in the hands of the physician

Often the critical evaluation of the drug to be administered is as important to the patient's recovery as is the diagnosis of his condition. In each case correct procedures can be determined only by the physician.

CHLOROMYCETIN is eminent among drugs at the disposal of the medical profession. Clinical findings attest that, in the hands of the physician, this widely used, broad spectrum antibiotic has proved invaluable against a great variety of infectious disorders.

Chloromycetin®

notably effective
well tolerated
broad spectrum antibiotic

The many hundreds of clinical reports on CHLOROMYCETIN emphasize repeatedly its exceptional tolerance as demonstrated by the infrequent occurrence of even mild signs and symptoms of gastrointestinal distress and other side effects in patients receiving the drug.

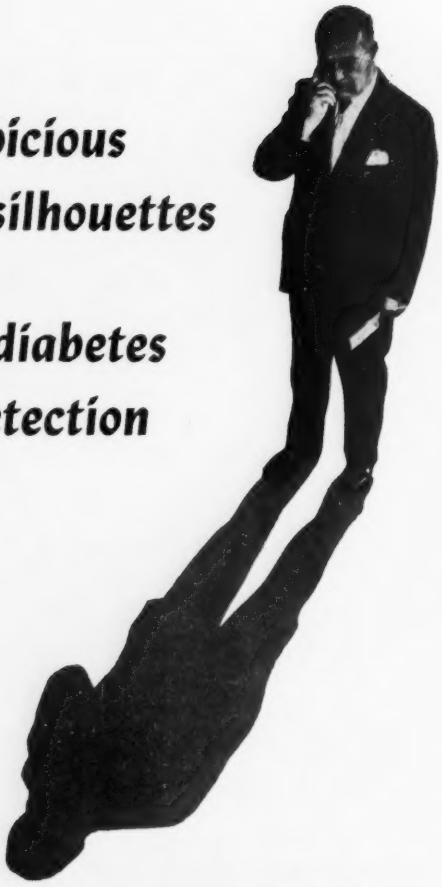
Similarly, the broad clinical effectiveness of CHLOROMYCETIN has been established, and serious blood disorders following its use are rare. However, it is a potent therapeutic agent, and should not be used indiscriminately or for minor infections—and, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in a variety of forms, including:
CHLOROMYCETIN Kapseals,® 250 mg., bottles of 16 and 100.
CHLOROMYCETIN Capsules, 100 mg., bottles of 25 and 100.
CHLOROMYCETIN Capsules, 50 mg., bottles of 25 and 100.
CHLOROMYCETIN Ophthalmic Ointment, 1%, ⅛-ounce collapsible tubes.
CHLOROMYCETIN Ophthalmic, 25 mg. dry powder for solution, individual vials with droppers.

MEDICAMENTA VERA · PD & CO.

Parke, Davis + Company
DETROIT, MICHIGAN

suspicious silhouettes in diabetes detection



Every overweight patient presents grounds for suspicion of diabetes. ". . among 1,900 men whose diabetes began after age 35, more than 80 per cent were overweight (5 per cent or more above average weight for age) before the onset of the disease."[1] In a recent survey the incidence of diabetes was found to be *5.7 per cent* in individuals over 35 who were 10 per cent or more overweight: among those whose weight was normal or below normal, only 2.4 per cent were diabetic.[2]

When a "suspicious silhouette" is seen, the physician suspecting diabetes can quickly and easily test for urine-sugar with *Clinitest* (Brand) Reagent Tablets. The test is simple, reliable and direct-reading. It is compact and portable, requiring no special apparatus and no external heating.

Clinitest Urine-sugar Analysis Set
No. 2155 UNIVERSAL MODEL

Plastic carrying case containing *Clinitest* Reagent Tablets (sealed in moisture-proof foil), test tube, dropper, instructions, analysis record and *Clinitest* Color Scale.

1. Desirable Weights for Men: Metropolitan Life Insurance Company, Pamphlet T5044, March 1951.
2. Look for Diabetes, Federal Security Agency, Public Health Service, Pamphlet GPO 83-34064.

CLINITEST

BRAND · REG. U. S. PAT. OFF.

to detect urine-sugar

AMES
COMPANY, INC., ELKHART, INDIANA

Ames Company of Canada, Ltd., Toronto

44452

A. M. A.
ARCHIVES OF INTERNAL MEDICINE

VOLUME 91 FEBRUARY 1953 NUMBER 2

COPYRIGHT, 1953, BY THE AMERICAN MEDICAL ASSOCIATION

ANTIBIOTIC RESISTANCE OF PATHOGENIC STAPHYLOCOCCI

Study of Five Hundred Strains Isolated at Boston City Hospital from October, 1951, to February, 1952

MAXWELL FINLAND, M.D.
AND
THOMAS H. HAIGHT, M.D.
With the technical assistance of Clare Wilcox and Marilyn K. Broderick
BOSTON

SOON AFTER interest in Fleming's penicillin was reawakened through the work of Chain and Florey [1] and their associates, there appeared evidence of the occurrence of penicillin-resistant strains of pathogenic staphylococci after exposure to penicillin both in vitro and in vivo.[2] In 1945, North and Christie [3] obtained 128 strains of staphylococci (88 coagulase producers and 40 not coagulase producers) from one hospital where penicillin had not been used and compared them with 31 coagulase-positive strains isolated from patients in another hospital where penicillin was being used extensively. The coagulase-positive strains from the former hospital were all inhibited by 1/8 unit or less, while the coagulase-negative ones were all completely inhibited by 1/2 unit or less. By contrast, only 13 of the strains from the hospital where penicillin was widely used were inhibited by less than 1 unit, and 17 required 2 to 80 units. Since that time many similar observations have been reported, particularly from hospitals in Britain, Australia, and this country [4]; all indicate an increasing incidence of penicillin-resistant staphylococci.

This study was aided by a grant from the United States Public Health Service.

From the Thorndike Memorial Laboratory and the Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1. Chain, E.; Florey, H. W.; Gardner, A. D.; Jennings, M. A.; Orr-Ewing, J.; Sanders, A. E., and Heatley, N. G.: Penicillin as a Chemotherapeutic Agent, Lancet **2**:226, 1940.

2. (*a*) Abraham, E. P., and others: Further Observations on Penicillin, Lancet **2**:177, 1941. (*b*) Rammelkamp, C. H., and Maxon, T.: Resistance of Staphylococcus Aureus to the Action of Penicillin, Proc. Soc. Exper. Biol. & Med. **51**:386, 1942. (*c*) Spink, W. W., and Ferris, V.: Penicillin-Resistant Staphylococci: Mechanisms Involved in the Development of Resistance, J. Clin. Invest. **26**:379, 1947.

3. North, E. A., and Christie, R.: Observations on the Sensitivity of Staphylococci to Penicillin, M. J. Australia **2**:44, 1945.

4. (*a*) Barber, M.: Coagulase-Positive Staphylococci Resistant to Penicillin, J. Path. & Bact. **59**:373, 1947; (*b*) Staphylococcal Infection Due to Penicillin-Resistant Strains, Brit. M. J. **2**:863, 1947. (*c*) Forbes, G. B.: Infection with Penicillin-Resistant Staphylococci in Hospital and General Practice, ibid. **2**:569, 1949. (*d*) Barber, M.; Hayhoe, F. G. J., and Whitehead, J. E. M.: Penicillin-Resistant Staphylococcal Infection in a Maternity Hospital, Lancet **2**:1120, 1949. (*e*) Rountree, P. M., and Thomson, E. F.: Incidence of Penicillin-Resistant and Streptomycin-Resistant Staphylococci in a Hospital, ibid. **2**:501, 1949. (*f*) Beigelman, P. M., and Rantz, L. A.: The Clinical Importance of Coagulase-Positive, Penicillin-Resistant Staphylococcus Aureus, New England J. Med. **242**:353, 1950. (*g*) Cairns, H. J. F., and Summers, G. A. C.: Penicillin-Resistant Staphylococci: Incidence in Relation to Length

(Footnote continued on next page)

The close correlation between penicillin resistance of staphylococci and their ability to produce penicillinase was first pointed out by Bondi and Dietz.[5] Among 115 strains which they studied, 99 which were inhibited by 0.15 unit of penicillin or less failed to produce penicillinase, whereas 16 which required 1.35 units or more for inhibition produced penicillinase. They found no correlation between penicillinase production and hemolysis, pigment production, or coagulase activity. Also of considerable interest is the report of the isolation of three "food-poisoning strains" of staphylococci which were naturally penicillin resistant (probably to more than 200 units per milliliter).[6]

During previous studies in this laboratory on the antibiotic spectra of pathogenic bacteria it was noted that different strains of staphylococci varied widely in their resistance to penicillin, whereas they were more or less uniform in their sensitivity to the other antibiotics with which they were tested. It was also determined that a profound change had taken place in the relative incidence of penicillin-sensitive and penicillin-resistant staphylococci, there having been few truly resistant strains in 1945 or earlier, whereas a significant proportion of strains isolated after 1946 were highly resistant. Aureomycin and chloramphenicol had only recently been introduced and had not yet come into wide use when that study was done, and the staphylococci studied at that time were uniformly sensitive to these antibiotics.[7]

The present study was undertaken for the purpose of evaluating the Staphylococcus problem at the Boston City Hospital with respect to the sensitivity of the strains currently being isolated to the antibiotics that are now widely used.

MATERIALS AND METHODS

The strains of Staphylococcus aureus included in the present study were obtained from patients under treatment for various infections at the Boston City Hospital. The majority of these patients had at one time or another received one or more of the antibiotics, but for the

of Stay in Hospital, Lancet **1**:446, 1950. (*h*) Rountree, P. M.; Barbour, R. G. H., and Thomson, E. F.: Incidence of Penicillin-Resistant and Streptomycin-Resistant Staphylococci in a Hospital, ibid. **1**:435, 1951. (*i*) Thompson, B. A., and Schwabacher, H.: The Incidence of Penicillin-Resistant Staphylococci in a Semi-Closed Community, J. Clin. Path. **4**:350, 1951. (*j*) Vogelsang, T. M.: The Incidence of Penicillin-Resistant Pathogenic Staphylococci Isolated from the Upper Respiratory Tract of Young Healthy Persons, Acta path. et microbiol. Scandinav. **29**:363, 1951. (*k*) Böe, J., and Vogelsang, T. M.: Penicillin-Resistant Pathogenic Staphylococci: Increasing Incidence of Resistant Strains in the Upper Respiratory Tract, ibid. **29**:368, 1951. (*l*) Rountree, P. M., and Barbour, R. G. H.: Nasal Carrier Rates of Staphylococcus Pyogenes in Hospital Nurses, J. Path. & Bact. **63**:313, 1951. (*m*) Summers, G. A. C.: Penicillin-Resistant Staphylococci: Distribution Among Outpatients, Lancet **1**:135, 1952. (*n*) Reiss, E.; Pulaski, E. J.; Amspacher, W. H., and Contreras, A. A.: Penicillin Sensitivity of Staphylococci, New England J. Med. **246**:611, 1952. (*o*) Wilson, R., and Cockcroft, W. H.: The Problem of Penicillin-Resistant Staphylococcal Infection, Canad. M. A. J. **66**:548, 1952. (*p*) Leyton, G. B.: Some Observations on Staphylococci and Their Resistance to Antibiotics, ibid. **67**:20, 1952.

5. Bondi, A., Jr., and Dietz, C. C.: Relationship of Penicillinase to the Action of Penicillin, Proc. Soc. Exper. Biol. & Med. **56**:135, 1944.

6. Mason, H. C.: Food-Poisoning Staphylococci and the Order of Their Resistance to Penicillin: Inhibition of Coagulase Production, J. Immunol. **51**:307, 1945.

7. Finland, M.; Frank, P. F., and Wilcox, C.: In Vitro Susceptibility of Pathogenic Staphylococci to 7 Antibiotics (Penicillin, Streptomycin, Bacitracin, Polymyxin, Aerosporin, Aureomycin and Chloromycetin), Am. J. Clin. Path. **20**:325, 1950.

purpose of these observations only those strains were included which were isolated from cultures obtained either at the time of admission, immediately prior to institution of therapy with some antibiotic, or before a change was made from one antimicrobial agent to another while the patient was in the hospital. The strains thus represented a wide cross section of the staphylococcal population as it appeared in patients entering or under treatment at this hospital.

The sources from which the strains were isolated are listed in Table 1. The sputum and material from the nose, throat, and ears were obtained from patients with active infections in the respiratory passages, and in general staphylococci were the only or the predominant organisms present in the cultures. The same statement is true of most of the strains obtained from skin lesions, wounds, postoperative infections, superficial ulcers, and so on, although other bacteria were often also present in abundance in these sources. The cultures of abscesses, blood, urine, and feces and those of material from patients with osteomyelitis were almost always pure cutures of hemolytic Staph. aureus. All the strains were isolated from single colonies; each was checked for its identifying characteristics before it was used in the study, and all were hemolytic on horse-blood agar, produced yellow pigment, and were coagulase-positive.

Sensitivity Tests.—The method for determining the sensitivity of the organisms to the various antibiotics was similar to that employed in previous tests in this laboratory. Groups of

TABLE 1.—*Sources of Strains of Staphylococci Studied at Boston City Hospital from October, 1951, to February, 1952*

Source	No. of Strains	% of Total
Respiratory tract (nose, throat sputum, ears)	185	37.0
Skin (wounds, ulcers, vesicles, exudative lesions)	124	24.8
Abscess and infected body cavities	57	11.4
Osteomyelitis	41	8.2
Urine	35	7.0
Feces (diarrhea)	33	6.6
Blood	25	5.0
All sources	500	100.0

strains, as they became available, were tested to all antibiotics simultaneously by a standard twofold agar plate dilution method.[8] The values for sensitivity are defined in terms of the end-points of growth and are expressed as the minimum concentration of antibiotics which produced complete inhibition of visible growth of the strains after 24 hours of incubation at 37 C., the concentrations being expressed in micrograms per milliliter in every instance.

Test for Penicillinase Production.—A modified Gots test for penicillinase production was used; details of this test are given elsewhere.[9] Briefly, the test consists of pouring plates with agar containing 0.01 ml. of a fully grown culture of Sarcina lutea and a concentration of penicillin (0.005 μg. per milliliter) which completely inhibits that organism but permits the growth of all staphylococcal strains. After rapid cooling and hardening of the agar, the cultures of staphylococci are streaked on the surface of the plates. The presence of visible colonies of Sarcina within the agar in the vicinity of the growth of the staphylococci indicates inactivation of penicillin and thus penicillinase production by the bacteria.

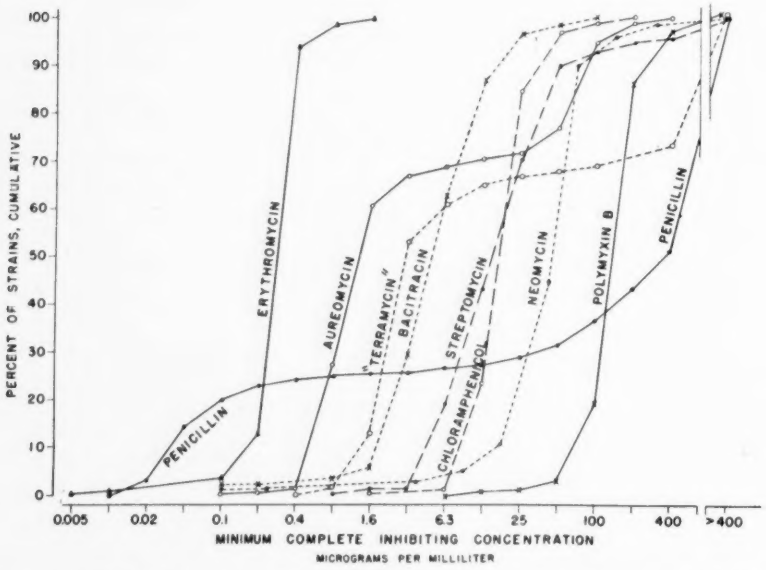
RESULTS

Antibiotic Spectrum of the Staphylococcus.—The results of the sensitivity tests carried out on 500 strains of staphylococci with nine antibiotics are shown in the accompanying chart in the same manner as in the earlier studies referred to.[7] It is

8. Jackson, G. G., and Finland, M.: Comparison of Methods for Determining Sensitivity of Bacteria to Antibiotics in Vitro, A. M. A. Arch. Int. Med. **88**:446, 1951.

9. Haight, T. H., and Finland, M.: Modified Gots Test for Penicillinase Production, Am. J. Clin. Path. **22**:806, 1952.

readily apparent that with certain of the agents, notably penicillin, aureomycin, and oxytetracycline ("terramycin"), the sensitivity of the organisms varied over a wide range of concentrations, some strains being highly susceptible, while others were highly resistant, to these antibiotics. Striking is the wide middle range of concentrations, between the highly sensitive and the highly resistant, which includes only 10 to 15% of the strains. This middle zone extends over a considerably wider range of concentrations for penicillin than for any of the other agents. This fact may be interpreted as indicating a marked change from the predominance of highly susceptible staphylococcal strains to a predominance of highly resistant ones. The distribution curves for the less effective, less popular, or less widely used agents, viz., streptomycin, neomycin, chloramphenicol, and polymyxin B, show much less variation from



Sensitivity of Staph. aureus to nine antibiotics, based on 500 pathogenic strains isolated at the Boston City Hospital from October, 1951, to February, 1952.

the standard cumulative distribution curve; the inhibiting concentrations of these agents for most of the strains fall within a relatively narrow range. This statement is particularly true of erythromycin, a new antibiotic which was recently shown to have marked activity against staphylococci[10]; this fact may be interpreted as indicating that no naturally occurring staphylococci of high or even moderate resistance to erythromycin were encountered in this study. The same observation has proved to be true thus far with respect to another new antibiotic, carbomycin (magna-

10. McGuire, J. M., and others: "Ilotycin," a New Antibiotic, Antibiotics & Chemother. **2**:281, 1952. Heilman, F. R.; Herrell, W. E.; Wellman, W. E., and Geraci, J. E.: Some Laboratory and Clinical Observations on a New Antibiotic, Erythromycin (Ilotycin), Proc. Staff Meet., Mayo Clin. **27**:285, 1952. Haight, T. H., and Finland, M.: Laboratory and Clinical Studies on Erythromycin, New England J. Med. **247**:227, 1952.

mycin),[11] which was not available at the time the 500 strains on which the chart is based were collected.

On a weight basis, the order of effectiveness of the antibiotics against the great majority of the collected strains of staphylococci, according to this spectrum, was approximately as follows: (1) erythromycin, (2) aureomycin, (3) oxytetracycline, (4) bacitracin, (5) streptomycin, (6) chloramphenicol, (7) neomycin, (8) polymyxin B, and (9) penicillin. About 20% of the strains, however, were more sensitive to penicillin than to any of the other agents, and for these strains penicillin would rank first.

Classification of Grades of Antibiotic Resistance.—For the purpose of further comparisons, it became necessary to adopt some arbitrary classification of sensitivity and resistance to the different antibiotics; this was needed, of course, only for the agents to which different strains showed significant variations in sensitivity and concerned only the antibiotics which have been in wide use. The classification chosen was related in part to the clinical attainability of blood or urine levels comparable

TABLE 2.—*Grades of Antibiotic Resistance Expressed in Terms of Minimum Completely Inhibiting Concentration (Micrograms per Milliliter), as Determined by a Twofold Plate-Dilution Test*

Antibiotic	Grade of Resistance		
	Sensitive (S)	Intermediate (I)	Resistant (R)
Penicillin	0.8 or less	1.6-12.5	25 or more
Aureomycin	3.1 or less	6.3-50	100 or more
Oxytetracycline	3.1 or less	6.3-50	100 or more
Chloramphenicol	6.3 or less	12.5-50	100 or more
Streptomycin	6.3 or less	12.5-50	100 or more

to the concentrations within the different grades, and in part it was arbitrary and based on convenience in subdividing the strains into distinct categories. The classification finally arrived at is given in Table 2.

The distribution of the 500 strains with respect to the grades of resistance as defined in this classification is shown for the five most important antibiotics in Table 3. It may be seen that only one-fourth of the strains were classified as sensitive to penicillin; almost all the rest were resistant, and only 2.2% were considered to be intermediate in their sensitivity. To aureomycin, about two-thirds of the strains were sensitive, almost one-fourth were resistant, and 9% were intermediate. Only a little more than half of the strains were sensitive to oxytetracycline, nearly one-third were resistant, and about 15% were intermediate in their susceptibility. There was greater uniformity with respect to chloramphenicol, as is evident from the chart; almost all the strains were graded as intermediate, and only a few were classified as either sensitive or resistant. The sensitivity to streptomycin was also fairly uniform; the great majority of strains were intermediate in their susceptibility, but 20% were classified as sensitive and 10% as resistant.

11. (*a*) Tanner, F. W., Jr.; English, A. R.; Lees, T. M., and Routien, J. B.: Some Properties of Magnamycin, a New Antibiotic, Antibiotics & Chemother. **2**:441, 1952. (*b*) Finland, M.; Wilcox, C.; Wright, S. S., and Purcell, E. M.: Cross-Resistance to Antibiotics: Effect of Exposures of Bacteria to Carbomycin or Erythromycin in Vitro, Proc. Soc. Exper. Biol. & Med. **81**:725, 1952.

Penicillinase Production by Staphylococci.—It is generally agreed that strains of Staph. aureus which are naturally resistant to penicillin or which acquire resistance during the course of therapy with penicillin produce penicillinase, whereas strains made resistant by exposures to penicillin in vitro do not do so.[12] One observation, however, lends credence to the view that some adaptively resistant strains may also produce penicillinase.[13] It seemed worth while to assess both these points in the present study.

By the modified Gots method as described above all strains of staphylococci were tested for their ability to produce penicillinase. The results are listed in Table 4; they show a striking relationship between the susceptibility of the strains to the inhibitory action of penicillin and their ability to produce penicillinase. All the resistant strains produced penicillinase, and none of the sensitive strains did so; a few strains of intermediate sensitivity, namely those inhibited by 3.1 to 6.3 γ per milliliter, showed variable responses.

TABLE 3.—*Distribution of 500 Strains of Staph. Aureus According to Grade of Resistance to Five Antibiotics Which Have Been in Common Use*

Antibiotic	Grade of Resistance*	No. of Strains	% of Strains
Penicillin	S	124	24.8
Penicillin	I	11	2.2
Penicillin	R	365	73.0
Aureomycin	S	337	67.4
Aureomycin	I	45	9.0
Aureomycin	R	118	23.6
Oxytetracycline	S	266	53.2
Oxytetracycline	I	73	14.6
Oxytetracycline	R	161	32.2
Chloramphenicol	S	6	1.2
Chloramphenicol	I	482	96.4
Chloramphenicol	R	12	2.4
Streptomycin	S	99	19.8
Streptomycin	I	351	70.2
Streptomycin	R	50	10.0

* As defined in Table 2.

For determination of the effect of resistance resulting from exposures to penicillin in vitro, 12 strains of staphylococci which were initially highly sensitive to penicillin were transferred daily by serial subculture on the surface of the agar plates containing increasing concentrations of penicillin. After 25 such transfers, most of

12. Bondi, A., Jr., and Dietz, C. C.: Penicillin Resistant Staphylococci, Proc. Soc. Exper. Biol. & Med. **60**:55, 1945. Frieden, E. H.; Whiteley, H. R., and Frazier, C. N.: Some Characteristics of Penicillin-Resistant Staphylococci, Texas Rep. Biol. & Med. **5**:74, 1947. Martin, T. D. M., and Whitehead, J. E. M.: Carriage of Penicillin-Resistant Staph. Pyogenes in Healthy Adults, Brit. M. J. **1**:173, 1949. Martyn, G.: Staphylococci in the Newborn; Their Coagulase Production and Resistance to Penicillin and Streptomycin, ibid. **1**:710, 1949. Chandler, C. A.; Davidson, V. Z.; Long, P. H., and Monnier, J. J.: Studies on Resistance of Staphylococci to Penicillin: The Production of Penicillinase and Its Inhibition by the Action of Aureomycin, Bull. Johns Hopkins Hosp. **89**:81, 1951. Spink and Ferris.[2e] Bondi and Dietz.[5]

13. Luria, S. E.: A Test for Penicillin Sensitivity and Resistance in Staphylococcus, Proc. Soc. Exper. Biol. & Med. **61**:46, 1946.

the strains required 100 γ or more of penicillin per milliliter for complete inhibition. Before these transfers were started and again daily after each subculture and after the end of the experiment, the strains were checked for their ability to produce penicillinase. None of the initially sensitive strains produced the enzyme, and it was not possible at any time during the transfers or at the conclusion of the experiment to demonstrate that the adaptively resistant organisms had acquired such a faculty. Interestingly enough, none of the resistant strains obtained after the subcultures in penicillin had lost their coagulase-producing ability, an observation confirming the earlier findings of others.[14] This is in contrast to the observations made with resistant strains derived by repeated subcultures on erythromycin-containing agar: some of the erythromycin-resistant strains lost their coagulase-producing property,[15] while others retained it.[16] Variable results were also obtained with resistant staphylococci obtained by repeated subcultures in carbomycin.[11b]

TABLE 4.—*Relationship Between Penicillinase Production and Penicillin Sensitivity in 500 Strains of Staphylococci*

Sensitivity to Penicillin, γ per Ml.	No. of Strains	
	Producing Penicillinase	Not Producing Penicillinase
0.02	0	18
0.04	0	53
0.1	0	29
0.2	0	14
0.4	0	6
0.8	0	4
1.6	0	1
3.1	1	3
6.3	2	1
12.5	3	0
25	10	0
50	14	0
100	24	0
200	31	0
400	40	0
>400	246	0
Totals	371	129

Correlation Between Antibiotic Sensitivity and Source of Strain.—Sherris and Florey [17] studied a number of strains of staphylococci from different sources and concluded that penicillin-sensitive strains produce types of lesions different from those produced by penicillin-resistant strains. The sensitive staphylococci were associated with acute and closed lesions and with deep-seated lesions which were either acute or chronic, whereas the penicillin-resistant strains were obtained primarily

14. Blair, J. E.; Carr, M., and Buchman, J.: The Action of Penicillin on Staphylococci, J. Immunol. **52**:281, 1946. Abraham and others.[2a] Bondi and Dietz.[5]

15. Haight, T. H., and Finland, M.: Resistance of Bacteria to Erythromycin, Proc. Soc. Exper. Biol. & Med. **81**:183, 1952.

16. Wright, S. S.; Purcell, E. M., and Finland, M.: Antibiotic Combinations and Resistance to Antibiotics: In Vitro Resistance of Bacteria to Erythromycin and Streptomycin, to be published. Purcell, E. M.; Wright, S. S., and Finland, M.: Antibiotic Combinations and Resistance to Antibiotics: Resistance of Staphylococci to Penicillin, Erythromycin, or Both, to be published.

17. Sherris, J. C., and Florey, M. E.: Relation of Penicillin Sensitivity in Staphylococci to Clinical Manifestations of Infection, Lancet **1**:309, 1951.

from superficial infections and were less often associated with signs of inflammation and suppuration. Since such a relationship is of profound importance from the therapeutic point of view, it was of interest to determine whether such a correlation existed among the 500 strains in this study. For this purpose, the strains were divided according to their sources, and the percentage of strains from each source showing the different grades of resistance to each of the antibiotics was calculated. The results are shown only for those antibiotics to which strains varied in resistance, namely for penicillin, aureomycin, and oxytetracycline, and they are listed in Table 5.

It is immediately apparent that, with few exceptions, there was no direct correlation between the grade of sensitivity of the staphylococci and the source from which they were obtained. This observation was true not only for penicillin but also for aureomycin and oxytetracycline. With the probable exception of the strains obtained from stool cultures, there were similar proportions of organisms sensitive and resistant to each of the three antibiotics. The larger proportion of resistant organisms

TABLE 5.—*Relationship Between Sources of Strains of Staph. Aureus and Grade of Their Resistance to Penicillin, Aureomycin, and Oxytetracycline**

Source of Strains ‡	No. of Strains	Grade † of Resistance to: Penicillin S	Penicillin I	Penicillin R	Aureomycin S	Aureomycin I	Aureomycin R	Oxytetracycline S	Oxytetracycline I	Oxytetracycline R
Respiratory tract	185	26	3	70	69	9	22	50	19	31
Skin	124	23	0	77	69	10	21	59	12	29
Abscesses	57	35	0	65	70	4	26	49	19	32
Osteomyelitis	41	22	7	71	83	7	10	66	17	17
Urine	35	29	0	71	66	14	20	60	9	31
Feces	33	9	0	91	21	15	64	21	0	79
Blood	25	16	8	76	76	8	16	68	8	24
All sources	500	25	2	73	67	9	24	53	15	32

* Five hundred strains isolated at Boston City Hospital from October, 1951, to February, 1952.
† As defined in Table 2; numbers indicate %.
‡ See also Table 1.

obtained from stool cultures is probably a reflection of the fact that the cultures were obtained from patients in whom staphylococcal diarrheas developed secondarily to oral antibiotic therapy, especially with oxytetracycline. The possibility that these were naturally resistant strains similar to the staphylococcal-enteritis strains described by Mason [6] could not be entirely excluded; if they were, however, it would be necessary to assume that they were originally present in the mouth or bowel in a latent state and then multiplied and became pathogenic during oral antibiotic therapy. It may also be worth noting that the lowest percentage of strains resistant to aureomycin and also to oxytetracycline were among those obtained from the purulent drainage in cases of osteomyelitis; the incidence of penicillin-resistant strains derived from this source was the same as for all sources. Almost all the patients had been treated with penicillin, and few had received either aureomycin or oxytetracycline.

Although the fact is not shown in Table 5, there was no correlation whatever between source of the staphylococci and grade of their resistance to any of the other antibiotics.

Correlation of Grades of Resistance as Between Pairs of Antibiotics.—It was of interest to determine whether there was any correlation between the susceptibility

of the strains of staphylococci to any one antibiotic and their sensitivity or resistance to any of the others. For this purpose it was not necessary to consider some of the antibiotics, namely, erythromycin, bacitracin, chloramphenicol, neomycin, and polymyxin, since the sensitivity of the different strains to any one of these agents was more or less uniform, as indicated in the chart. The correlations between the incidence of the different grades of resistance among the 500 strains of staphylococci with respect to any two antibiotics for each of which significant variations in resistance did occur, namely, penicillin, aureomycin, oxytetracycline, and streptomycin, are shown in Table 6.

With respect to penicillin and aureomycin there was a rather striking relationship. None of the penicillin-sensitive or intermediate strains were resistant to aureomycin; or, to put it another way, all the aureomycin-resistant strains were also

TABLE 6.—*Correlation of Grades of Resistance Between Pairs of Antibiotics**

		Aureomycin			
		S	I	R	All
Penicillin	S	119	5	0	124
	I	11	0	0	11
	R	207	40	118	365
	All	337	45	118	500

		Oxytetracycline			
		S	I	R	All
Penicillin	S	88	35	1	124
	I	6	5	0	11
	R	172	33	160	365
	All	266	73	161	500

		Streptomycin			
		S	I	R	All
Penicillin	S	28	85	11	124
	I	3	6	2	11
	R	68	260	37	365
	All	99	351	50	500

		Oxytetracycline			
		S	I	R	All
Streptomycin	S	82	14	3	99
	I	168	48	135	351
	R	16	11	23	50
	All	266	73	161	500

		Streptomycin			
		S	I	R	All
Aureomycin	S	96	211	30	337
	I	3	37	5	45
	R	0	103	15	118
	All	99	351	50	500

		Oxytetracycline			
		S	I	R	All
Aureomycin	S	258	66	13	337
	I	6	7	32	45
	R	2	0	116	118
	All	266	73	161	500

* For definition of grades of resistance (S, I, and R), see Table 2. Figures indicate number of strains.

resistant to penicillin. Essentially, the same relationship is seen to exist between penicillin and oxytetracycline. On the contrary, the greater proportion of the penicillin-resistant strains were either sensitive or intermediate in their susceptibility to aureomycin or oxytetracycline; also, the strains which were sensitive to aureomycin or oxytetracycline included about twice as many penicillin-resistant as penicillin-sensitive strains. This relationship may reflect the fact that aureomycin and oxytetracycline have, in the great majority of cases, been administered to patients who had previously been treated with penicillin or who were known to have penicillin-resistant strains at the outset and were, therefore, treated with either aureomycin or oxytetracycline.

Between streptomycin and each of the other three antibiotics there was no correlation whatever; the strains showed essentially the same distribution among the different grades of resistance to each of the antibiotics independently of their resistance to the other.

On the other hand, the correlation between sensitivity and resistance to aureomycin and to oxytetracycline was very close and might perhaps have been even closer had it not been for the fact that aureomycin had an appreciably greater inhibitory effect than oxytetracycline on many of the strains, as indicated in the chart and in Table 7. Only 2 of the 118 aureomycin-resistant strains were sensitive, and the others were all resistant to oxytetracycline; among the oxytetracycline-resistant strains 72% were resistant, 20% were intermediate, and only 8% were sensitive to aureomycin. Conversely, among the 266 oxytetracycline-sensitive strains, only 2 were resistant and 6 others intermediate in their susceptibility to aureomycin; while among the 337 aureomycin-sensitive strains, 77% were sensitive, 19% were intermediate and only 4% were resistant to oxytetracycline. The intermediate strains reflected the greater inhibitory action of aureomycin; of the 73 strains which were intermediate in their susceptibility to oxytetracycline, 90% were sensitive, the rest were intermediate, and none were resistant to aureomycin. By

TABLE 7.—*Relationship Between Sensitivity to Aureomycin and to Oxytetracycline*

Oxytetracycline, γ per Ml.	Aureomycin, γ per Ml.											
	0.4 or Less	0.8	1.6	3.1	6.3	12.5	25	50	100	200	400 or More	Total
0.8	..	1*	7	..	..	..	..	..	..	..	..	8
1.6	3	22	27	1	..	..	..	..	..	..	..	53
3.1	7	75	95	20	1	5	..	..	2	..	..	205
6.3	1	11	20	8	4	..	..	..	..	..	..	44
12.5	..	6	5	3	3	..	..	..	..	..	..	17
25	1	4	4	..	..	..	..	..	..	..	..	9
50	..	1	2	..	..	..	..	..	..	..	..	3
100	..	1	1	2	..	..	..	..	..	..	..	4
200	..	2	1	1	1	1	1	..	..	..	..	7
400 or more	1	2	0	2	..	1	3	25	91	21	4	150
Total	13	125	162	37	9	7	4	25	93	21	4	500

* Figures indicate numbers of strains.

contrast, 32, or 71%, of the 45 aureomycin-intermediate strains were resistant and the rest were either intermediate or sensitive to oxytetracycline. This close correlation between the action of aureomycin and that of oxytetracycline is consistent with: (1) the similar, if not identical, antimicrobial spectrum of these two antibiotics; (2) their comparable activity against individual strains; (3) the marked cross resistance which has been noted to develop as a result of repeated subcultures of various organisms in the presence of each of these antibiotics separately,[18] and

18. Pansy, F. E.; Khan, P.; Pagano, J. F., and Donovick, R.: The Relationship Between Aureomycin, Chloramphenicol, and Terramycin, Proc. Soc. Exper. Biol. & Med. **75**:618, 1950. Kaipainen, W. J.: Does Induced Resistance of Bacteria to One Antibiotic Result in Simultaneous Sensitivity Changes to the Other Antibiotics? Ann. med. exper. et biol. Fenniae (Supp. 1) **29**:1, 1951. Fusillo, N. H., and Romansky, M. J.: The Simultaneous Increase in Resistance of Bacteria to Aureomycin and Terramycin upon Exposure to Either Antibiotic, Antibiotics & Chemother. **1**:107, 1951. Monnier, J. J., and Schoenbach, E. B.: The Resultant Sensitivity of Microorganisms to Various Antibiotics After Induced Resistance to Each of These Agents, Antibiotics & Chemother. **1**:472, 1951. Gocke, T. M., and Finland, M.: Cross-Resistance to Antibiotics: Effect of Repeated Exposure of Bacteria to Aureomycin, Terramycin, Chloramphenicol or Neomycin on the Resistance to All of These Antibiotics and to Streptomycin and Penicillin, J. Lab. & Clin. Med. **38**:719, 1951.

(4) the recent demonstration of the close similarity between the chemical structures of these two agents.[19]

There was some evidence of cross resistance between neomycin and streptomycin which is not shown in the table. Of the 12 strains which were found to require 50 or 100 γ of neomycin per milliliter for inhibition (these were the highest required for any of the strains), 9 were resistant to more than 100 γ per milliliter of streptomycin. The reverse of this observation was not so striking; of the 50 strains which were streptomycin-resistant, as defined in Table 2 (that is, they required 100 γ or more per milliliter for inhibition), only these 9 strains were neomycin-resistant. These in vivo findings are, therefore, somewhat similar to the in vitro observations which indicated less cross resistance to neomycin from exposure to streptomycin than streptomycin resistance from exposure to neomycin.[20]

Relationship of Grade of Resistance to Previous Therapy.—An attempt was made to determine whether the grade of resistance of the staphylococci to any of the antibiotics could be correlated with the previous antibiotic therapy of the patients from whom the strains were cultured. For this purpose all the current and previous hospital and outpatient records of the patients yielding the strains were thoroughly reviewed. In many current cases the patient, and in some instances the local physician, were again questioned to verify the details of such therapy. Information which was considered to be fairly complete and reliable was obtained with respect to 335 of the strains. The correlations between the grades of resistance of these 335 strains to each of five antibiotics and the previous therapy with the different antibiotics is shown in Table 8. Of the antibiotics which inhibited almost all the strains more or less uniformly, only chloramphenicol is included, both for comparison and because of the cross resistance to that agent which has been demonstrated to develop when organisms are repeatedly exposed to aureomycin or oxytetracycline in vitro.[18]

There were 106 strains from patients who, as far as could be determined, had not previously received any antibiotic. Most of these strains were obtained from cultures made either for outpatients or for hospitalized patients at the time of admission, before therapy was started. Some of these patients had previously taken sulfonamides at home or in the hospital. More than one-half the strains were resistant to penicillin, but only 10% or fewer were resistant to any of the other agents. There were 41 additional strains from patients who had received only penicillin in the past but had received none from nine months to more than six years prior to isolation of the Staphylococcus. These strains likewise were obtained, for the most part, from outpatients or from admission cultures. In this group, 73% of the strains were penicillin-resistant, and the proportion of strains resistant to aureomycin and oxytetracycline was apparently greater than it was among strains from patients who had never received an antibiotic.

19. Hochstein, F. A., and others: Terramycin: The Structure of Terramycin, J. Am. Chem. Soc. **74**:3708, 1952. Stephens, C. R., and others: Terramycin: Structure of Aureomycin and Terramycin, ibid **74**:4976, 1952. Waller, C. W., and others: Degradation of Aureomycin: Aureomycin and Anhydroaureomycin, ibid. **74**:4981, 1952.

20. Haight, T. H.; Wilcox, C., and Finland, M.: Cross-Resistance to Antibiotics: Effect of Repeated Exposures of Bacteria to Streptomycin or Neomycin on the Resistance to Both of These and to 6 Other Antibiotics, J. Lab. & Clin. Med. **39**:637, 1952.

There were 99 strains derived from patients who were either receiving penicillin at the time the culture was made or had been treated with that antibiotic recently but presumably had received no other antibiotic. In this group, 92% of the strains were resistant to penicillin, and 18% and 24% were resistant to aureomycin and oxytetracycline, respectively.

Only 21 strains were from patients who had received or were receiving both penicillin and streptomycin. All were resistant to penicillin; about one-half were resistant to aureomycin, two-thirds to oxytetracycline, and one-third to streptomycin. This group of strains, though small, contained the greatest proportion of strains resistant to all four of these antibiotics.

Patients who had received either aureomycin or oxytetracycline or both in addition to penicillin yielded 45 strains, and only 23 strains were isolated from patients

TABLE 8.—*Relationship of Antibiotic Resistance of Strains of Staph. Aureus to Previous Antibiotic Therapy of the Patients from Whom They Were Cultured*

Previous Antibiotic Therapy	No. of Strains	Grade of Resistance * to: Penicillin S	Penicillin I	Penicillin R	Aureomycin S	Aureomycin I	Aureomycin R	Oxytetracycline S	Oxytetracycline I	Oxytetracycline R	Chloramphenicol S	Chloramphenicol I	Chloramphenicol R	Streptomycin S	Streptomycin I	Streptomycin R
A None	106	45†	0	55	88	5	7	69	21	10	2	97	1	19	74	7
B Penicillin (more than 9 mo. before)	41	27	0	73	78	7	15	56	27	17	2	93	5	19	71	10
C Penicillin	99	15	3	82	75	7	18	64	12	24	0	96	4	20	69	11
D Penicillin & streptomycin	21	0	0	100	19	29	52	14	10	76	0	95	5	5	62	33
E Penicillin & aureomycin, oxytetracycline, or both	45	20	0	80	40	18	42	33	11	56	2	96	2	18	71	11
F Aureomycin and/or oxytetracycline	23	13	0	87	30	17	52	22	9	69	0	91	9	13	78	9
G All penicillin (B-E)	208‡	17	1	82	62	11	27	50	14	36	1	95	4	18	69	13
H All aureomycin and/or oxytetracycline (E & F)	72§	17	0	83	36	17	47	29	10	61	1	93	6	15	74	11
All strains	500	25	2	73	67	9	24	53	15	32	1	97	2	20	70	10

* As defined in Table 2.

† Percentage of strains from patients in same antibiotic group.

‡ Includes one strain from a patient who also received aureomycin and streptomycin and one from a patient who received oxytetracycline and streptomycin (in addition to penicillin).

§ Includes two strains noted above (†) and two additional strains, one from a patient who had been treated with streptomycin and one from a patient who had received chloramphenicol (in addition to oxytetracycline).

who had been treated with aureomycin or oxytetracycline but allegedly had received no penicillin. The percentages of strains resistant to each of these three antibiotics were high in both these groups and were somewhat higher with respect to all three, even penicillin, in the group with no history of treatment with penicillin. The difference may not be significant, but it suggests the possibility of some exposure of the patients or of their organisms to penicillin, in spite of the negative history; such an exposure may conceivably have occurred in persons from whom the patient acquired these strains. Moreover, some of these patients received aureomycin or oxytetracycline only after earlier strains had been tested and found to be penicillin-resistant.

These findings suggest that previous treatment with antibiotics may be of great importance in establishing strains of staphylococci resistant to the antibiotics used. They also suggest that some strains of staphylococci are either naturally resistant to one or more antibiotics or acquire such resistance by exposures in other hosts.

from whom the strains are acquired by contact. The latter possibility is suggested more directly by several epidemiological studies of the spread of antibiotic-resistant staphylococci in hospitals.[21]

Comparison of Antibiotic-Sensitivity of Multiple Strains from the Same Patient.—More than one strain of hemolytic, coagulase-positive Staphylococcus were obtained from each of 49 patients; they were isolated either from different sources

TABLE 9.—*Antibiotic Sensitivity of Multiple Strains of Staph. Aureus Obtained from the Same Patient at the Same or at Different Times*

Patient	Strain	Date * Isolated	Source	Previous Antibiotic Therapy †	Sensitivity in γ/Ml.				
					Penicillin	Aureomycin	Oxytetracycline	Chloramphenicol	Streptomycin
I. W.	1	10/7	Abscess, buttock	P, A	200	100	>400	25	25
	23	10/30	Sputum	P, A	100	1.6	1.6	25	25
	42	11/6	Ulcer, leg	P, A	>400	200	>400	25	50
M. M.	68	11/14	Infected bursa	—	0.04	1.6	6.3	25	12.5
	94	11/14	Skin wound	—	400	200	>400	25	12.5
P. S.	161	12/7	Pustule	P, A	>400	50	>400	12.5	25
	162	12/7	Sputum	P, A	>400	50	>400	12.5	25
	165	12/7	Blood	P, A	0.04	1.6	3.1	6.3	25
J. T.	221	12/20	Vomitus	P, O	>400	100	>400	12.5	25
	250	12/20, A	Blood	P, O	>400	0.8	1.6	12.5	25
	251	12/20, P	Blood	P, O	>400	0.8	1.6	25	25
	257	12/23	Throat	P, O, S	>400	700	>400	0.4	50
	259	12/23	Blood	P, O, S	>400	3.1	3.1	25	50
G. T.	198	12/19	Throat	P >16 mo.	>400	3.1	100	25	>400
	338	1/9	Sputum	P >16 mo.	3.1	1.6	50	25	25
W. M.	249	12/20	Synovial fluid	P	0.09	3.1	1.6	25	12.5
	339	1/9	Feces	P, T	400	50	>400	25	>400
W. C.	348	1/11	Wound	P	>400	1.6	3.1	50	0.1
	378	1/11	Blood	P	0.8	0.8	3.1	25	25
M. McL.	228	12/23	Throat	P	100	1.6	3.1	25	12.5
	346	1/10	Pleural fluid	P	0.09	1.6	6.3	50	6.3
	379	1/11	Osteomyelitis	P	0.04	0.8	1.6	25	200
F. W.	351	1/11	Nose	P	>400	>100	400	50	25
	381	1/11	Sputum	P	200	1.6	3.1	25	50
G. W.	375	1/15	Sputum	P >10 mo.	400	1.6	25	25	25
	394	1/16	Sputum	P >10 mo.	0.8	1.6	6.3	25	25
S. N.	391	1/16	Sputum	A	0.09	3.1	3.1	50	25
	395	1/16	Blood	A	100	1.6	6.3	25	12.5
D. M.	423	1/21	Carbuncle	—	0.04	1.6	3.1	25	50
	434	1/23	Carbuncle	P	>400	0.8	3.1	25	12.5
N. M.	409	1/21	Throat	—	>400	100	>400	25	100
	451	1/23	Urine	—	>400	3.1	3.1	25	6.3
B. M.	396	1/16	Blood	—	0.04	1.6	3.1	25	25
	450	1/20	Blood	P	>400	3.1	3.1	25	6.3
	441	1/24	Abscess	P, A	>400	100	>400	25	25
	454	1/24, A	Blood	P, A	>400	100	>400	25	12.5
	455	1/24, P	Blood	P, A	>400	200	>400	25	25
F. K.	482	2/1	Urine	A	>400	1.6	1.6	25	6.3
	499	2/2	Stool	A	>400	200	>400	50	>400
J. K.	426	1/23	Throat	P	>400	100	>400	25	25
	429	1/23	Sputum	P	>400	1.6	3.1	25	12.5
	459	1/26	Sputum	P, A	>400	100	>400	25	25
	500	2/5	Eye	P, A	>400	1.6	3.1	12.5	6.3
	501	2/5	Scrotum	P, A	>400	6.3	6.3	12.5	6.3

* October, November, and December are 1951; January and February are 1952. A indicates a. m., and P, p. m.
† P indicates penicillin; A, aureomycin; O, oxytetracycline, and S, streptomycin. The duration noted after P indicates the interval after penicillin was last given.

at the same time or from the same or different sources at different times. In each instance, however, the Staphylococcus was either the only or the predominant organism in the culture or was present in abundance with the other organisms. Two strains were obtained from each of 31 patients, and three, four, and five strains were isolated from each of 11, 4, and 3 patients, respectively. Of the total of 116

21. North and Christie.[3] Barber, Hayhoe, and Whitehead.[4d] Rountree and Thomson.[4e] Beigelman and Rantz.[4f]

strains isolated from these 49 patients, 55 strains were obtained from 23 patients, each of whom contributed 2 or 3 strains which were identical in their susceptibility to all the antibiotics. There were also two patients from each of whom were isolated three strains having identical reactions to all the antibiotics except that one of the three strains from each patient was highly resistant to streptomycin, whereas the other two were sensitive; as far as could be ascertained, neither of these patients had received streptomycin and the streptomycin-resistant variant was obtained after the patient had received only penicillin.

The pertinent data relating to 44 other strains isolated from 16 patients are listed in Table 9; they serve to illustrate the findings in the remaining cases. There was no entirely consistent or uniform pattern exhibited by the different strains obtained from the same patient. In general, however, the sensitive strains were more often obtained from blood or sputum or from deep-seated foci or body cavities, whereas resistant organisms were often isolated from the more superficial lesions. In some cases, a change from sensitive to resistant strains followed the institution of therapy with the agent to which the later strains were resistant, as shown by patients D. M., B. M., and F. K., but this was not the rule.

COMMENT

It is evident that strains with high degrees of penicillin resistance were predominant among the pathogenic staphylococci isolated during the fall and winter of 1951-1952. It is also apparent that there was a considerable and significant increase in the proportion of strains which were highly resistant to aureomycin and oxytetracycline, particularly the latter. While it is true that some strains of staphylococci obtained from blood, infected body cavities, or deep-seated foci were sensitive to one or more antibiotics to which other strains, obtained from other sources at the same or different times, were resistant, this situation was not the rule. Thus, the proportions of penicillin-resistant or oxytetracycline-resistant staphylococci were not significantly different from those of strains obtained from other sources, and aureomycin-resistant strains were only slightly less frequent among strains isolated from blood. Only the fecal staphylococci showed a significantly higher proportion of strains resistant to penicillin, aureomycin, and oxytetracycline as compared with strains derived from any other source.

The origin of the resistant strains is by no means clear in all cases. In some patients they were obtained only after antibiotic therapy, and some of these strains exhibited resistance specifically to the antibiotic that was used or to a closely related one. That this is not always the case is clear from the data presented so far as they can be considered as reliable with respect to the total history of previous antibiotic therapy. Exposure of the organism to the antibiotics, either directly by treatment of the patient from whom the resistant strain was obtained or indirectly by acquisition of the strain from a carrier or another infected patient who, in turn, received such therapy, must be postulated to account for the great majority of the resistant strains. The fact that there has been an increase in the proportion only of strains of staphylococci resistant to antibiotics which are widely used and only in places where they are so used lends credence to this view. The relatively low incidence of strains resistant to streptomycin, chloramphenicol, or any other antibiotic which in this hospital had been used infrequently or not at all further supports this view,

since resistance of staphylococci to those agents has been readily induced in vitro and would probably emerge during treatment if such agents were used extensively and over long periods.[22]

Cross resistance probably plays a considerable role in the case of aureomycin and oxytetracycline. In vitro, cross resistance between these two agents and chloramphenicol also occurs, but it is usually not so striking; the present data would indicate that it is not very significant clinically, at least with respect to the acquisition of chloramphenicol resistance from exposure to aureomycin or oxytetracycline. There is also some evidence, though not too convincing, of cross resistance between streptomycin and neomycin similar to that which can be demonstrated following repeated exposures of bacteria to these antibiotics in vitro.[20]

SUMMARY AND CONCLUSIONS

Five hundred strains of hemolytic, coagulase-positive Staph. aureus isolated from clinical material at the Boston City Hospital from October, 1951, to February, 1952, were tested for sensitivity to nine antibiotics. From the results of these tests an "antibiotic spectrum" was constructed (Chart) which indicates at a glance the relative susceptibility of these strains to each of the antibiotics and also permits direct comparisons of the relative activity of the different antibiotics against all the strains.

The most striking findings were the marked increases in the incidence of penicillin-resistant strains and the significant increase over previous findings in the proportion of strains resistant to aureomycin and oxytetracycline ("terramycin"), particularly the latter. About three-fourths of the strains were resistant to penicillin, one-fourth were resistant to aureomycin, and one-third were resistant to oxytetracycline.

The close correlation between penicillin resistance and penicillinase production by recently isolated strains of staphylococci was confirmed. Except for a slight overlap of seven strains which were inhibited by 3.1 or 6.3 γ of penicillin per milliliter, all strains resistant to higher concentrations were penicillinase producers, while those sensitive to lower concentrations were not.

There was no close correlation between the source of the strains and their antibiotic resistance; the fecal strains, however, had a higher proportion resistant to penicillin, aureomycin, and oxytetracycline than did strains isolated from any other source.

There was a close correlation between resistance to aureomycin and to oxytetracycline when allowance is made for the relatively lower inhibitory action of the latter on a large proportion of the strains. There was no correlation between the grades of susceptibility to streptomycin and to any of the other antibiotics. On the other hand, strains that were resistant to aureomycin or to terramycin were all resistant to penicillin; the reverse, however, was not true.

22. Further evidence along this line was presented by Birnstingl, Shooter and Hunt (Brit. M. J. **2**:253, 1952) who studied 200 strains from skin or subcutaneous lesions of outpatients at the time of their first visit or when a lesion was first opened. Only a small proportion of these strains were penicillin-resistant (16% resistant to more than 1 unit) and none were resistant to aureomycin, streptomycin, chloramphenicol, or oxytretracycline.

While there was some relation between the incidence of antibiotic-resistant strains and use of the corresponding antibiotics in treatment of the patients from whom the strains were isolated, the correlation was not a close one. However, the data do suggest that while previous antibiotic therapy of any given patient may be an important factor in the occurrence of strains resistant to that antibiotic, the widespread use of antibiotics may be of equal or greater importance in the increase in incidence of staphylococci which are resistant to those antibiotics; such strains may become or remain pathogenic and retain their resistance when they are disseminated and acquired by patients who have themselves not received such antibiotics.

Examples are cited of multiple strains of staphylococci having varying grades of resistance to different antibiotics and having been isolated from the same patient either at the same time from different sources or at different times from the same or different sources. There appeared to be some relation between antibiotic resistance of some of these strains and their sources or the previous antibiotic therapy of the patients from whom they were isolated, but such a relationship was not observed for most of the strains.

LIVER COMA, WITH PARTICULAR REFERENCE TO MANAGEMENT

MICHAEL M. KARL, M.D.
ROY A. HOWELL, M.D.
JAMES H. HUTCHINSON, M.D.
AND
FRANK J. CATANZARO, M.D.
ST. LOUIS

COMA HAS long been recognized as an ominous manifestation of liver disease and as a frequent mode of death. In an attempt to learn more regarding etiologic factors, pathogenesis, chemical changes, and clinical course, 58 cases of liver disease characterized by coma were studied. It was hoped that a rational program of therapy could be formulated to improve the discouraging results noted in treating this condition to date.

Fifty-eight cases of cirrhosis complicated by hepatic coma were selected from the records of the St. Louis City Hospital. All but one of the patients had died. Nearly all had been observed by one of us. Patients with lethargy or only mild stupor were not included, nor were patients in coma associated with massive hemorrhage. All but one of the patients had been in coma at least 24 hours. Reports of liver biopsies or autopsies were available in 41 cases.

ETIOLOGICAL FACTORS

Incidence.—Inasmuch as these were selected cases, no accurate estimation of incidence is possible. During the period of study, 758 patients with cirrhosis of the liver were admitted to the St. Louis City Hospital. The incidence of cirrhosis in autopsy material at this hospital is reported as 2.2%.[1] Elsewhere, coma has been reported as complicating cirrhosis in from 16% [2] to 42% [3] of the cases studied.

Sex and Age.—Men predominated over women, 39 to 19. The ages ranged from 31 to 74 years for men, with an average of 54.6, and from 36 to 80 for women, with an average of 53.6 years; 68% of all patients studied were between the ages of 40 and 59 years.

From the Department of Internal Medicine, Washington University School of Medicine, and the Unit I (Washington University) Medical Service, at the St. Louis City Hospital.

1. Wade, L. J.: Recent Advances in the Therapy of Cirrhosis of the Liver, M. Clin. North America **29**:479, 1945.

2. Eppinger, H., cited in Lichtman, S. S.: Diseases of the Liver, Gallbladder, and Bile Ducts, Ed. 2, Philadelphia, Lea & Febiger, 1949, p. 619.

3. Snell, A. M., and Butt, H. R.: Hepatic Coma: Observations Bearing on Its Nature and Treatment, Tr. Am. Physicians **56**:321, 1941.

Nutrition and Alcohol.—Deficient nutrition and alcohol as prime factors in producing liver disease have been emphasized many times.[4] Their role seems especially important in patients who lapse into liver coma. Of the 58 patients studied, 40 gave histories of poor nutrition, 3 of only fair nutrition, and 11 of adequate nutrition. For four no information was available. Fifty patients gave a history of excessive alcoholic intake and four of moderate intake. Only four had apparently not partaken of alcoholic beverages. In 16 patients, near starvation seemed actually to precipitate the onset of coma, while an alcoholic debauch seemed to produce coma in 12 patients.

Other Contributing Factors.—Fifteen patients presented a history of jaundice prior to the development of cirrhosis. Since the role of hepatitis as an etiological factor in cirrhosis is now generally accepted,[5] this history seems significant. Only two patients were exposed to hepatotoxins, one to carbon tetrachloride and one to naphthalene. Major infection apparently precipitated coma in four patients and surgical operations in three. How abdominal operations may influence liver function adversely has been pointed out by Geller and Tagnon.[6]

TABLE 1.—*Incidence of Signs and Symptoms in Fifty-Eight Cases of Hepatic Coma*

Signs and Symptoms	% of Cases	Signs and Symptoms	% of Cases
Anorexia	89	Hemangiomata	57
Nausea and vomiting	62	Atrophic testes	51
Mental and neurological changes	48	Evidence of collateral circulation	38
Abdominal pain	43	Neurological signs	28
Diarrhea	33	Hemorrhoids	24
Tarry stools	26	Liver palms	17
History of hematemesis	19	Melena	17
Ascites	84	Fetor hepaticus	16
Fever	81	Splenomegaly	14
Jaundice	76	Gynecomastia	13
Heptomegaly	76	Hematemesis	9
Edema	67	Hydrothorax	5

Hemorrhage from varices or elsewhere in the gastrointestinal tract is well recognized as a factor in producing coma. Cases of such hemorrhage, however, have been excluded from this study.

CLINICAL DATA

The incidence of symptoms obtained from the patients' history and the objective signs observed on physical examination are given in Table 1.

4. (*a*) Boles, R. S., and Clark, J. H.: The Role of Alcohol in Cirrhosis of the Liver: A Clinical and Pathological Study Based on 4,000 Autopsies, J. A. M. A. **107**:1200, 1936. (*b*) Patek, A. J.; Post, J.; Ratnoff, O. D.; Mankin, H., and Hillman, R. W.: Dietary Treatment of Cirrhosis of the Liver: Results in 124 Patients Observed During a 10 Year Period, ibid. **138**:543, 1948. (*c*) Jolliffe, N., and Jellinek, E. M.: Vitamin Deficiencies and Liver Cirrhosis in Alcoholism, Quart. J. Stud. Alcohol **2**:544, 1941. (*d*) Olsen, A. Y.: A Study of Dietary Factors, Alcoholic Consumption, and Laboratory Findings in 100 Patients with Hepatic Cirrhosis and 200 Non-Cirrhotic Controls, Am. J. M. Sc. **220**:477, 1950.

5. Howard, R., and Watson, C. J.: Antecedent Jaundice in Cirrhosis of the Liver, Arch. Int. Med. **80**:1, 1947. Koszalka, M. F.; Lindert, M. C. F.; Snodrass, H. M., and Lerner, H. B.: Hepatitis and Its Sequelae, Including the Development of Portal Cirrhosis: Observations on 100 Cases, ibid. **84**:782, 1949.

6. Geller, W., and Tagnon, H. J.: Liver Dysfunction Following Abdominal Operations: Significance of Postoperative Hyperbilirubinemia, Arch. Int. Med. **86**:908, 1950.

Less than one-third of the patients were in coma at the time of admission. Mental and neurological changes preceded coma in 48% of the patients. These included confusion, disorientation, delirium, restlessness, choreiform and athetoid movements, agitation, lethargy, and hallucinosis. Gradually, these changes were followed by lapse into coma. Fetor hepaticus developed, icterus increased, and the temperature rose sometimes as high as 105 F. The size of the liver at times decreased markedly and rapidly. Objective neurological signs such as tremors, muscle rigidity and spasm, nuchal rigidity, a positive Babinsky sign, dilated pupils, increased deep tendon reflexes, clonus, and occasionally convulsions developed. Secondary infec-

TABLE 2.—*Incidence of Abnormal Laboratory Findings in Fifty-Eight Cases of Hepatic Coma*

Finding	% of Cases	
Cephalin-cholesterol flocculation (3 or 4+)		100
Abnormal sulfobromophthalein sodium retention (greater than 10%)		94
10-30%	22	
31-50%	47	
Greater than 50%	25	
Prothrombin time prolonged (less than 60%)		94
40-60%	39	
Less than 40%	55	
Low cholesterol esters (less than 55%)		93
40-55%	32	
20-40%	18	
Less than 20%	43	
Azotemia (blood urea nitrogen greater than 20 mg. per 100 ml.)		91
20-50 mg.	73	
Greater than 50 mg.	18	
Elevated serum bilirubin (2-32.5 mg. per 100 ml.)		88
Low serum albumin (less than 3.5 gm. per 100 ml.)		87
3-3.5 gm. per 100 ml.	19	
2-3 gm.	49	
Less than 2 gm.	19	
High serum globulin (greater than 3 gm. per 100 ml.)		85
3-4 gm.	42	
4-5 gm.	37	
Greater than 5 gm.	6	
Anemia (red cells less than 4,000,000)		83
Low total cholesterol (less than 125 mg. per 100 ml.)		69
75-125 mg.	44	
Less than 75 mg.	25	
Elevated thymol turbidity (greater than 5 units)		65
5-10 units	48	
Greater than 10 units	17	
Leucocytosis (more than 10,000 white cells)		50

tions such as bronchopneumonia, cellulitis, pyelonephritis, peritonitis, and cholecystitis developed in 48% of the patients. Coma persisted as long as 13 days, but 46% of the patients were in coma less than 5 days.

LABORATORY DATA

The abnormal laboratory data noted are given in Table 2.

The cephalin-cholesterol flocculation test was positive in all the cases studied, while the thymol turbidity test was abnormal in only 65%. This difference is in accord with observations reported elsewhere that the cephalin-cholesterol flocculation test is more consistently altered in cirrhosis than the thymol turbidity test.[7]

7. Watson, C. J., and Rappaport, E. M.: Comparison of Results Obtained with Hanger Cephalin-Cholesterol Flocculation Test and MacLagan Thymol Turbidity Test in Patients with Liver Disease, J. Lab. & Clin. Med. **30**:983, 1945. Kunkel, H. G.: Value and Limitations of the Thymol Turbidity Test as an Index of Liver Disease, Am. J. Med. **4**:201, 1948.

It is interesting to note further that only 17% of the abnormal thymol turbidity tests reported gave a result higher than 10 units. This finding lends weight to the impression that the thymol turbidity test is a reflection of the abnormal function of regenerating liver cells, as suggested by Popper and associates.[8] The combination of a positive cephalin-cholesterol flocculation test and a low thymol turbidity reaction in cirrhosis with impending coma may, therefore, be construed as a bad prognostic sign.

Consistent with many previous observations is the low serum albumin and the elevated serum globulin content. The relation of these values to the production of ascites has been stressed by Post and Patek[9] and Ralli and associates.[10] but Hiller, Huffman, and Levey[11] have pointed out that protein concentrations in the plasma do not necessarily reflect the amount of total circulating proteins, since the circulating-blood volume is frequently increased. The significance of this observation in relation to therapy is discussed hereafter.

Cholesterol and cholesterol ester determinations were carried out in only half the cases studied; when the results were available, they served as a valuable prognostic aid, as reported by Stueck and his associates.[12] It was frequently noted that as the patient lapsed into coma, the level of cholesterol esters fell markedly.

Eighty-three per cent of the patients studied had a red cell count of less than 4,000,000. Since blood indices were not studied routinely, the nature of the anemia was not known. However, Wintrobe[13] and Berman and co-workers[14] have reported that such anemias are usually normocytic or macrocytic. When blood loss is present, the anemia may be microcytic. A tendency toward leucopenia has been reported in cirrhosis, but in this series only one patient had a white cell count of less than 5,000.

As pointed out elsewhere,[15] there is nothing in the laboratory studies that would distinguish liver coma from any other type of severe liver disease. It should be noted, however, that the incidence of abnormal hepatic laboratory tests is high, so high that one is not secure, even in a cirrhotic patient in attributing coma to liver

8. Popper, H.; Steigmann, F.; Meyer, K.; Kozoll, D. D., and Franklin, M.: Correlation of Liver Function and Liver Structure: Clinical Applications, Am. J. Med. **6**:278, 1949.

9. Post, J., and Patek, A. J., Jr.: Serum Proteins in Cirrhosis of the Liver: Relation to Prognosis and to Formation of Ascites, Arch. Int. Med. **69**:67, 1942.

10. Ralli, E. P.; Robson, J. S.; Clarke, D. H., and Hoagland, C. L.: Factors Influencing Ascites in Patients with Cirrhosis of the Liver, J. Clin. Invest. **2**:316, 1945.

11. Hiller, G. I.; Huffman, E. R., and Levey, S.: Studies in Cirrhosis of the Liver: Relationship Between Plasma Volume, Plasma Protein Concentrations, and Total Circulating Proteins, J. Clin. Invest. **28**:322, 1949.

12. Stueck, G. H.; Rubin, S. H.; Clarke, D. H.; Graef, I., and Ralli, E. P: Studies on Patients with Cirrhosis of the Liver: Plasma and Liver Lipid Distribution and Its Relation to the Pathology of the Liver, Am J. Med. **5**:188, 1948.

13. Wintrobe, M. M.: Relation of Disease of the Liver to Anemia: Type of Anemia, Response to Treatment, and Relation of Type of Anemia to Histopathologic Changes in Liver, Spleen and Bone Marrow, Arch. Int. Med. **57**:289, 1936.

14. Berman, L.; Axelrod, A. R.; Horan, T. N.; Jacobson, S. D.; Sharp, E. A., and Vonder Heide, E. C.: The Blood and Bone Marrow in Patients with Cirrhosis of the Liver, Blood **4**:511, 1949.

15. (*a*) Murphy, T. L.; Chalmers, T. C.; Eckhardt, R. D., and Davidson, C. S.: Hepatic Coma: Clinical and Laboratory Observations on 40 Patients, New England J. Med. **239**:605, 1948. (*b*) Snell and Butt.[3]

disease unless hepatic tests are markedly altered. Coma in a cirrhotic patient without such altered findings should be carefully reevaluated for other causes.

PATHOLOGICAL FINDINGS

The pathological findings for 39 patients who had complete autopsies are recorded in Tables 3 and 4.

The microscopic appearances of the liver sections showed marked variations. In some sections the classic microscopic appearance of Laennec's cirrhosis was noted, with its characteristically altered architectural pattern. In these sections, there were irregular islands of hepatic tissue with varying amounts of distorted

TABLE 3.—*Autopsy Findings in Thirty-Nine Cases of Hepatic Coma*

Finding	No. of Cases		Finding	No. of Cases	
Lung pathology		33	Testicular atrophy (among 24 men)		6
Bronchopneumonia	24		Pancreatitis, acute		3
Congestion	10		Pancreatic fibrosis		3
Infarction	2		Renal pathology		19
Pleural effusion	2		Tubular degeneration, general	10	
Ascites		29	Swelling of proximal tubules	3	
Varices		22	Swelling of distal tubules	1	
Cholecystitis, chronic		14	Bile nephrosis	3	
Cholelithiasis		9	Glomerulonephritis	1	
Gastrointestinal bleeding		8	Pyelonephritis	1	

TABLE 4.—*Weight of Spleens and Livers in Thirty-Nine Cases of Hepatic Coma*

Liver, Gm.	No. of Cases	Spleen, Gm.	No. of Cases
720-1,000	6	120-250	8
1,000-1,500	12	250-500	21
1,500-2,000	7	500-900	10
2,000-2,500	10		
2,500-3,000	2		
3,000-3,500	1		
5,390	1		

regenerating cells at the periphery surrounded by dense connective tissue. The portal areas in some sections showed biliary proliferation and round-cell infiltration. Fatty infiltration was often prominent, but there was little evidence of necrosis (Fig. 1).

In other sections the liver parenchyma had been completely replaced by fatty vacuolization, to the point that hepatic cells were not demonstrable (Fig. 2). There was little evidence of any inflammatory process and no evidence of regeneration. Occasionally a few hyaline degenerated cells could be made out around the portal areas. This type of lesion resembled that described by Mallory as "alcoholic cirrhosis."[16]

Still other sections showed extensive areas of centrilobular necrosis with marked cellular infiltration. Periportal necrosis with regenerating cells and fibrosis, while present, was not conspicuous. The microscopic appearance suggested that these changes were due to an acute hepatitis superimposed on an old chronic process

16. Mallory, F. B.: Cirrhosis of Liver, New England J. Med. **206**:1231, 1932.

(Figs. 3 and 4). It is significant that many of the patients gave a history of an alcoholic debauch prior to their last hospital admission; some had ingested "canned heat" or other toxic alcohols.

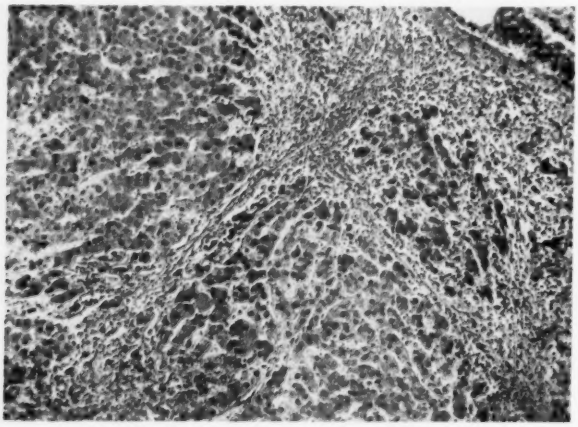


Fig. 1.—Laennec's cirrhosis, with typical irregular islands of hepatic cells, many distorted by regeneration, and surrounded by dense connective tissue. Portal areas show biliary proliferation and round-cell infiltration.

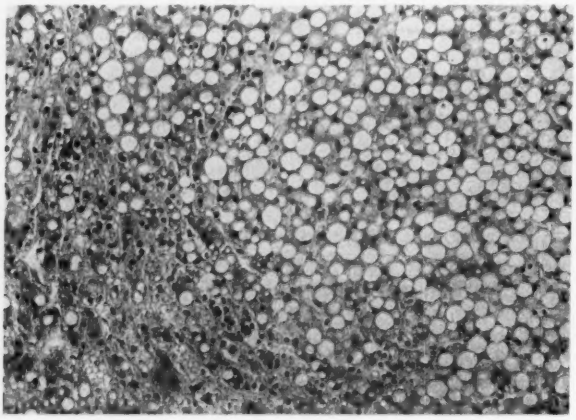


Fig. 2.—Cirrhosis of liver, with almost complete replacement of parenchyma with fatty vacuolization.

The central nervous system has been studied in patients with liver disease in the hope that some lesion might be discovered which is specific for hepatic coma. Watson [17] suggests that areas of perivascular demyelination and endothelial proliferation may represent evidence of hepatic encephalopathy. Our experience and

17. Watson, C. J.: The Prognosis and Treatment of Hepatic Insufficiency, Ann. Int. Med. **31**:405, 1949.

the experience of others [18] has indicated that these changes are nonspecific. They may include edema of brain substance, congestion of vessels, perivascular mononuclear infiltration (Fig. 5), and minute focal hemorrhages throughout the brain substance (Fig. 6).

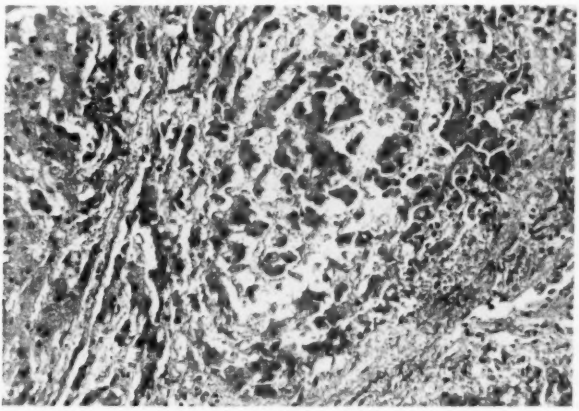


Fig. 3.—Cirrhosis of liver, with centrilobular necrosis.

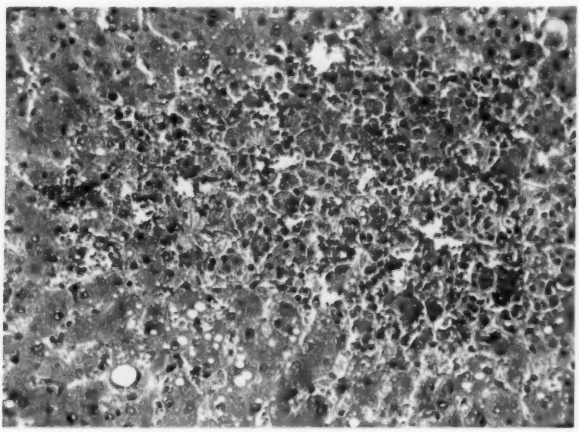


Fig. 4.—Cirrhosis of liver, with necrosis and marked cellular infiltration.

Likewise, no specific renal lesion was found in patients who had exhibited oliguria or anuria. Sections of the kidney either were normal or showed evidence of bile nephrosis, lower nephron nephrosis (Fig. 7), or intercapillary glomerulo-

18. Wood, D. A.: Pathologic Aspects of Acute Epidemic Hepatitis with Especial Reference to Early Stages: Report of Series of 10 Cases, Including Case in Which There Was Spontaneous Rupture of Spleen and 6 Cases of Fulminating Disease in Patients Who Had Been Wounded Several Months Previously, Arch. Path. **41**:345, 1946. Lucke, B.: The Pathology of Fatal Epidemic Hepatitis, Am. J. Path. **20**:471, 1944.

nephritis (Fig. 8) as described by Patek, Seegal, and Bevans.[19] Glomerular sclerosis resembling the Kimmelstiel-Wilson lesion as described by Baxter and Ashworth[20] was not seen. These observations would seem to support the contention of Lichtman and Sohval[21] and Snavely[22] that the description of a specific hepatorenal syndrome is not justified.

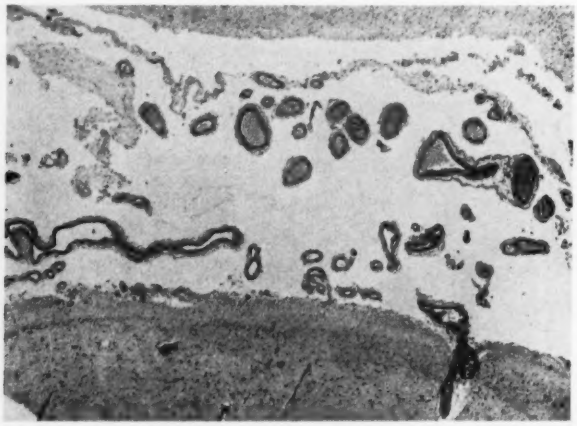


Fig. 5.—Edema of meninges and congestion of vessels in brain of a patient with cirrhosis who died in coma.

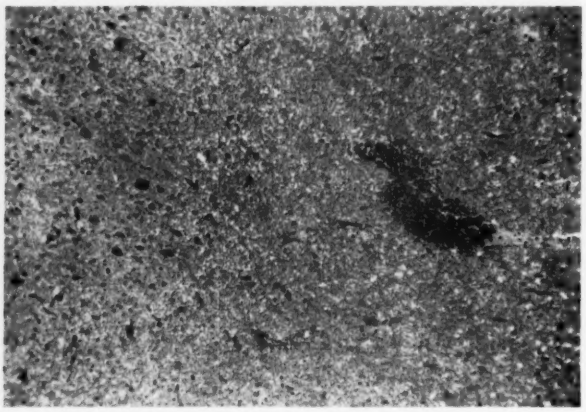


Fig. 6.—Congestion and focal hemorrhage in brain of a patient with cirrhosis who died in coma.

19. Patek, A. J., Jr.; Seegal, D., and Bevans, M.: Coexistence of Cirrhosis of the Liver and Glomerulonephritis, Am. J. M. Sc. **221**:77, 1951.

20. Baxter, J. H., and Ashworth, C. T.: Renal Lesions in Portal Cirrhosis, Arch. Path. **41**:476, 1946.

21. Lichtman, S. S., and Sohval, A. H.: Clinical Disorders with Associated Hepatic and Renal Manifestations, with Especial Reference to So-Called "Hepatorenal Syndrome," Am. J. Digest. Dis. **4**:26, 1937.

22. Snavely, J. R.: Hepatic Factors in Salt and Water Metabolism, Am. J. M. Sc. **223**:96, 1952.

MANAGEMENT

In view of the fact that two-thirds of the patients lapsed into coma while being treated in the hospital and all but one died, it seemed desirable to review the treatment used and to search the literature for any theoretical or clinical studies that might suggest better methods of therapy. Many forms of treatment were employed, including the use of special diets, lipotropic substances, and glucose; parenteral

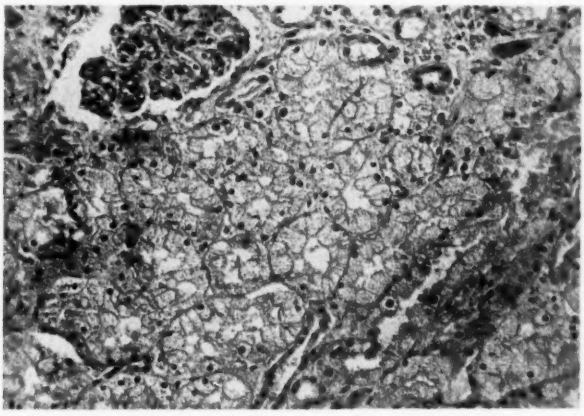


Fig. 7.—Swelling of convoluted renal tubules.

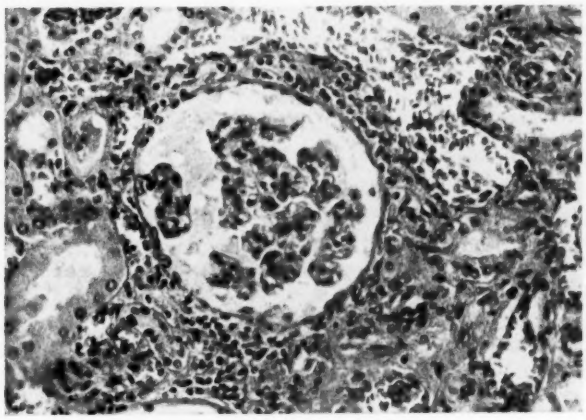


Fig. 8.—Intercapillary glomerulonephritis.

administration of proteins; transfusions of whole blood and washed red cells; administration of vitamins, liver extract, antibiotics, and mercurials; repeated paracenteses, and sedation.

Diet.—Patek has long advocated nutritious diet as the most important therapeutic tool in treating cirrhosis, recommending approximately 139 gm. of protein,

365 gm. of carbohydrate, and 175 gm. of fat daily.[23] Fleming and Snell[24] recommend 110 gm. of protein, 350 to 500 gm. of carbohydrate, and only 50 gm. of fat. There seems little evidence to suggest that such marked fat restriction is necessary or advantageous. With comatose patients, it becomes necessary to resort either to tube feedings or to parenteral feedings. The dangers of precipitating bleeding from varices or causing aspiration pneumonia seem more theoretical than real in our experience and rarely contraindicate the use of tube feedings.

Glucose.—Snell and Butt[3] recommend administration of glucose by continuous drip. They gave, daily, 3,000 to 4,000 cc. containing 50 to 100 mg. of thiamine hydrochloride and 250 to 500 mg. of nicotinic acid, with encouraging results. Bollman[25] has been unable to prove that glucose is beneficial in the case of liver injury and has suggested that it may be harmful. In this connection, it should be pointed out that several patients in this study who had received large quantities of glucose in water showed a marked drop in blood electrolytes. They had not had paracenteses or mercurial diuretics to account for low salt and potassium levels and must be considered to have had electrolyte dilution on the basis of water intoxication. This problem may become more complicated when cirrhosis is associated with metabolic alkalosis on the basis of excessive vomiting. Excessive administration of glucose and water without correction of other electrolytes in the presence of hypochloremic alkalosis may produce coma that bears no relation to concomitant cirrhosis (Case 1). It would seem that such changes resulting from excessive parenteral glucose therapy without consideration of electrolyte deficiencies have at times precipitated coma and have perhaps been a factor in producing the so-called hepatorenal syndrome.

Vitamins.—Since cirrhosis is generally considered to be a deficiency disease, it seems reasonable to supply vitamin supplements. Again, during coma the oral administration of vitamins becomes impractical. Parenteral administration of vitamins totaling several times the daily requirements is advisable. Recent work by György with experimental animals indicates that vitamin B_{12} may have strong lipotropic activity in fatty livers.[26] The parenteral administration of vitamin K seems clearly indicated when the prothrombin level is low, although it is rare that the prothrombin response is satisfactory in the face of grave liver damage. It has been shown that the pyruvic acid level in the blood and spinal fluid rises in direct proportion to the degree of liver failure and that the administration of thiamine does not check this rise.[27]

---

23. Patek, A. J., Jr., and Post, J.: Treatment of Cirrhosis of the Liver by a Nutritious Diet and Supplements Rich in Vitamin B Complex, J. Clin. Invest. **20**:481, 1941. Patek and others.[4b]

24. Fleming, R. G., and Snell, A. M.: Portal Cirrhosis with Ascites: Analysis of 200 Cases with Special Reference to Prognosis and Treatment, Am. J. Digest. Dis. **9**:115, 1942.

25. Bollman, J. L.: Liver Glycogen and the Protection of Liver Cells, in Transactions of the Seventh-Eighth Conference on Liver Injury, 1948-1949, edited by F. W. Hoffbauer, New York, Josiah Macy, Jr., Foundation, 1949, p. 116.

26. György, P.: Effects of Antibiotics and Vitamin B_{12} in Cirrhosis and Necrosis of the Liver, in Liver Disease, Ciba Clinical Symposia, Summit, N. J., Ciba Pharmaceutical Products, Inc., 1951, p. 81.

27. Amatuzio, D. S., and Nesbitt, S.: Study of Pyruvic Acid in Blood and Spinal Fluid of Patients With Liver Disease With and Without Hepatic Coma, J. Clin. Invest. **29**:1486, 1950.

Parenteral Administration of Proteins.—In the case of comatose patients with severe liver damage, the desirability of supplying proteins parenterally is apparent. While patients with cirrhosis may show some clinical improvement on low protein diets with negative nitrogen balance, morphologic improvement appears only when adequate protein is provided and a positive nitrogen balance is maintained.[28]

It seems reasonably conclusive that serum albumin is of little or no value for producing sustained diuresis, reducing ascites, or improving liver function[29] and that it may even induce fatal hemorrhage[30] or pulmonary edema.[31]

The advisability of giving amino acids parenterally to patients with severe liver disease is open to question, since there is evidence that badly damaged livers lose some of their ability to deaminize proteins. Stadie and Van Slyke,[32] Roman,[33] and Greene[34] have all reported that elevations of blood amino acid levels occur only in acute liver failure unassociated with cirrhosis. Dent and Walshe,[35] on the other hand, have demonstrated markedly elevated amino acids in the urine of five patients with cirrhosis dying in coma. Walshe[36] also has found increased amino acids in the blood, urine, and spinal fluid of patients dying in hepatic coma. On the other hand, improvement in liver function has been reported following the daily administration of 50 to 100 gm. of amino acids intravenously.[37]

Electrolytes.—Cirrhotic patients retain salt and show impaired renal excretion of sodium regardless of amount or route of saline therapy.[38] That retention of sodium

28. Eckhardt, R. D.; Zamcheck, N.; Sidman, R. L.; Gabuzda, G. J., and Davidson, C. S.: Effect of Protein Starvation and of Protein Feeding on the Clinical Course, Liver Function, Liver Histochemistry of 3 Patients with Active Fatty Alcoholic Cirrhosis, J. Clin. Invest. **29**:227, 1950.

29. Patek, A. J.; Mankin, H.; Colcher, H.; Lowell, A., and Earl, D. P., Jr.: The Effects of Intravenous Injection of Concentrated Human Serum Albumin upon Blood, Plasma, Ascites, and Renal Functions in 3 Patients with Cirrhosis of the Liver, J. Clin. Invest. **27**:135, 1948.

30. Faloon, W. W.; Eckhardt, R. D.; Murphy, T. L.; Cooper, A. M., and Davidson, C. S.: An Evaluation of Human Serum Albumin in the Treatment of Cirrhosis of the Liver, J. Clin. Invest. **28**:583, 1949.

31. Watson, C. J., and Greenberg, A.: Certain Effects of Salt Poor Human Albumin in Cases of Hepatic Disease, Am. J. M. Sc. **217**:651, 1949.

32. Stadie, W. C., and Van Slyke, D. D.: The Effect of Acute Yellow Atrophy on Metabolism and on the Composition of the Liver, Arch. Int. Med. **25**:693, 1920.

33. Roman, B.: Acute Yellow Atrophy of the Liver, Arch. Path. **4**:399, 1927.

34. Greene, C. H.: Liver and Biliary Tract: Review for 1940, Arch. Int. Med. **67**:867, 1941.

35. Dent, C. E., and Walshe, J. M.: Amino Acid Metabolism in Liver Disease, in Liver Disease, Ciba Clinical Symposia, Summit, N. J., Ciba Pharmaceutical Products, Inc., 1951, p. 22.

36. Walshe, J. M.: Observations on the Symptomatology and Pathogenesis of Hepatic Coma, Quart. J. Med. **20**:421, 1951.

37. Eckhardt, R. D.; Faloon, W. W., and Davidson, C. S.: Improvement of Active Liver Cirrhosis in Patients Maintained with Amino Acids Intravenously as the Source of Protein and Lipotropic Substances, J. Clin. Invest. **28**:603, 1949.

38. Ralli and others.[19] Goodyer, A. V. N.; Relman, A. S.; Lawrason, F. D., and Epstein, F. H.: Salt Retention in Cirrhosis of Liver, J. Clin. Invest. **29**:973, 1950. Farnsworth, E. B., and Krakusin, J. S.: Electrolyte Partition in Patients with Edema of Various Origins: Qualitative and Quantitative Definition of Cations and Anions in Hepatic Cirrhosis, J. Lab. & Clin. Med. **33**:1545, 1948.

is general is demonstrated by the fact that both saliva and sweat excretion studies reveal very little sodium.[39] Renal excretion is decreased despite normal glomerular filtration and renal plasma flow [38b] and can be increased by the administration of mercurial diuretics.[40] These features suggest that sodium retention may possibly be related to hormonal effects on the tubules. In any event, retention of salt is certainly an important factor in the formation of ascites and edema and forms the basis for the present concept that a low salt diet (200 to 600 mg.) will help control these symptoms.[41] However, it should be pointed out that apathy, weakness, delirium, a rising nonprotein nitrogen content, and coma may be precipitated by hyponatremia resulting from too vigorous salt restriction accompanied by repeated removal of large amounts of ascitic fluid [42] (Case 2). It has also been suggested that potentiating meralluride (mercuhydrin®) with ammonium chloride in cirrhosis may produce clinically significant hypokalemia with normal plasma sodium and chloride concentrations, as manifested by anorexia, drowsiness, weakness, and prostration.[43]

The recent introduction of cation exchange resins as an adjunct in treating ascites offers new hazards. Hypokalemia and hyponatremia have been noted in patients treated with resins (Case 3). In addition, Gabuzda reports that resins containing ammonium ions may induce a neurological disturbance resembling early liver coma despite normal serum electrolytes, perhaps owing to an accumulation of ammonia in the blood.[44]

Antibiotics.—Since infection is such an important factor in precipitating or complicating hepatic coma, the forceful use of antibiotics seems indicated. In addition, there is evidence to show that aureomycin, particularly, may prevent or retard hepatic necrosis.[45] If there is reason to suspect from the clinical course or laboratory findings that necrosis is a feature in a patient with coma, it would seem advantageous to administer aureomycin intravenously. Clinical reports on the favorable

39. Eisenmenger, W. J.; Blondheim, S. H.; Bongiovanni, A. M., and Kunkel, H. G.: Electrolyte Studies on Patients with Cirrhosis of the Liver, J. Clin. Invest. **29**:1491, 1950.

40. Faloon, W. W.; Eckhardt, R. D.; Cooper, A. M., and Davidson, C. S.: The Effect of Human Serum Albumin, Mercurial Diuretics, and a Low Sodium Diet on Sodium Excretion in Patients with Cirrhosis of the Liver, J. Clin. Invest. **28**:595, 1949.

41. Layne, J. A., and Schemm, F. R.: The Use of a High Fluid Intake and a Low-Sodium Acid-Ash Diet in the Management of Portal Cirrhosis with Ascites, Gastroenterology **9**:705, 1947. Ricketts, W. E.: Observations on Portal Cirrhosis with Ascites, Ann. Int. Med. **34**:37, 1951. Lowe, C. R., and Overy, D. C.: An Evaluation of Rigid Dietary Sodium Restriction in the Management of Ascites in Cirrhosis of the Liver, ibid. **34**:1396, 1951. Morrison, L. M.: Response of Cirrhosis of Liver to Intensive Combined Therapy, ibid. **24**:465, 1946.

42. Nelson, W. P., III; Rosenbaum, J. D., and Strauss, M. B.: Hyponatremia in Hepatic Cirrhosis Following Paracentesis, J. Clin. Invest. **30**:738, 1951.

43. Hilton, J. G.: Effects of Mercurial Diuresis in Patients with Ascites Due to Cirrhosis, Am. J. Med. **12**:311, 1952.

44. Gabuzda, G. J.; Phillips, G. B., and Davidson, C. S.: Reversible Toxic Manifestations in Patients with Cirrhosis of the Liver Given Cation-Exchange Resins, New England J. Med. **246**:124, 1952.

45. György, P.; Stokes, J.; Smith, W. H., and Goldblatt, H.: Studies on the Use of Aureomycin in Hepatic Disease: The Effect of Aureomycin on Experimental Dietary Hepatic Necrosis, Am. J. M. Sc. **220**:6, 1950.

effect of such therapy have appeared in the literature.[46] Conversely, recent studies have suggested that large doses of aureomycin administered intravenously may actually cause fatty infiltration of the liver.[47] Gabuzda, Jackson, and Grigsby [48] have recently reported that the administration of aureomycin to undernourished men was associated with an increase in urinary nitrogen and weight loss. This observation suggests that the administration of aureomycin might tend to invalidate other efforts made to improve nitrogen balance in liver coma.

Crude Liver Extracts.—Ralli and co-workers [49] have reported favorable results from specially prepared crude liver extracts, as first suggested by Labby and associates.[50] She believed that crude liver contained many growth-promoting factors that aided tissue regeneration, that it might play some part in reducing the amount of antidiuretic factors in the urine, and that it helped the appetite. In addition, Drill and Hall [51] have demonstrated the lipotropic effect of crude liver on hepatic injury in rats. Doses gradually increasing to as high as 50 cc. have been used. We have been able to use intravenously without ill effects ordinary crude liver injection prepared for intramuscular use when we diluted it to 1,000 cc. Murphy and co-workers [15a] have stated that crude liver has been of little value in their cases of liver coma.

Lipotropic Agents.—Clinical reports indicate that the use of lipotropic substances, such as methionine and choline, seems at times to exert a favorable response in cirrhosis.[52] On the other hand, Davidson and Gabuzda maintain that "there is no statistically valid clinical evidence that the addition of choline or methionine to

46. Farquhar, J. D.; Stokes, J.; Whitlock, C. M.; Bluemle, L. W., and Gambescia, J. M.: Studies on the Use of Aureomycin in Hepatic Disease: Note on Aureomycin Therapy in Hepatic Coma, Am. J. M. Sc. **220**:166, 1950. Schaffer, J. M.; Bluemle, L. W., Jr.; Sborov, V. M., and Neefe, J. R.: Studies on Use of Aureomycin in Hepatic Disease: Aureomycin Therapy in Chronic Liver Disease, with Note on Dermal Sensitivity, ibid. **220**:173, 1950. Goldbloom, R. S., and Steigmann, F.: Aureomycin Therapy in Hepatic Insufficiency, Gastroenterology **18**:93, 1951.

47. Sborov, V. M., and Sutherland, D. A.: Fatty Liver Following Aureomycin and Terramycin Therapy in Chronic Hepatic Disease, Gastroenterology **18**:598, 1951. Lepper, M. H.; Wolfe, C. K.; Zimmerman, H. J.; Caldwell, E. R., Jr.; Spies, H. W., and Dowling, H. F.: Effect of Large Doses of Aureomycin on Human Liver, A. M. A. Arch. Int. Med. **88**:271, 1951; Effect of Large Doses of Aureomycin, Terramycin, and Chloramphenicol on the Livers of Mice and Dogs, ibid. **88**:284, 1951.

48. Gabuzda, G. J.; Jackson, G. G., and Grigsby, M. E.: Effect of Aureomycin upon Nitrogen Balance and Urinary Riboflavin Excretion in Undernourished Men, read before the American Society for Clinical Investigation, Forty-Fourth Meeting, Atlantic City, N. J., May 5, 1952.

49. Ralli, E. P.; Leslie, S. H.; Stueck, G. H.; Shorr, H. E.; Robson, J. S.; Clarke, D. H., and Laken, B.: The Course of Cirrhosis of the Liver in Patients Treated with Large Doses of Liver Extract Intravenously: Study of 112 Cases; 44 Control Cases, 68 Cases Treated with Liver Extract Intravenously, Medicine **28**:301, 1949

50. Labby, D. H.; Shank, R. E.; Kunkel, H. J., and Hoagland, C. L.: Intravenous Therapy of Cirrhosis of the Liver, J. A. M. A. **133**:1181, 1947.

51. Drill, V. A., and Hall, C. A.: Lipotropic Effect of Liver Extract and Other Supplements in Dietary Induced Liver Injury in Rats, Am. J. M. Sc. **219**:197, 1950.

52. Steigman, F.: Efficacy of Lipotropic Substances in Treatment of Cirrhosis of Liver J. A. M. A. **137**:239, 1948. Morrison, L. M.: New Methods of Therapy in Cirrhosis of the Liver, ibid. **134**:673, 1947. Barker, W. H.: Modern Treatment of Cirrhosis of the Liver, M. Clin. North America **29**:273, 1945.

a nutritious diet induces a more rapid, more complete, or more certain recovery than diet alone." [53] Others have also maintained that the addition of choline did not accelerate the rate of fat clearance from the liver.[54] Observations of Cornatzer and Cayer [55] indicate that lipotropic substances caused an increase in phospholipid synthesis in cirrhotic but not in normal persons. More recent studies, however, have shown that this increase does not occur in cirrhotic persons unless fatty infiltration is present.[56] Drill and Hall [51] have pointed out that crude liver extract is as effective a lipotropic agent as choline, and György [57] has demonstrated that vitamin B_{12} in large doses likewise has a strong lipotropic action.

Sedatives.—Since the early stage of hepatic coma is often attended by delirium, restlessness, and hallucinosis, sedation is at times necessary. Coma has apparently been precipitated in patients with severe liver injury by the injudicious use of opiates and meperidine hydrochloride (demerol hydrochloride®), which are detoxified by the liver.[58] Short-acting barbiturates, such as secobarbital (seconal®) or pentobarbital (nembutal®), also fall into this group.[59] Paraldehyde has been indicted as a dangerous drug in the case of hepatic coma because approximately 75% of it is excreted by the liver.[60] However, even phenobarbital, which has been recommended, is known to show only 25% excretion in the urine, the remainder apparently beng detoxified by the liver. Of the barbiturates, only barbital is excreted almost entirely by the kidneys. From these observations, it is apparent that there is no ideal sedative for use in hepatic coma, that paraldehyde and phenobarbital show roughly equal degrees of detoxification by the liver, and that of the two paraldehyde has a greater margin of safety and shorter duration of action. When parenteral sedation is needed, sodium phenobarbital would appear to be the drug of choice. Either barbital or paraldehyde may be administered by stomach tube, while paraldehyde can be administered advantageously by rectum.

Correction of Anemia.—The anemia of liver disease is usually normocytic or macrocytic [61] but may be microcytic when hemorrhage is present. The degree of

53. Davidson, C. S., and Gabuzda, G. J., Jr.: Medical Progress: Nutrition and Disease of the Liver, New England J. Med. **243**:779, 1950.

54. Kessler, B. J.; Seife, M., and Lisa, J. R.: Use of Choline Supplements in Fatty Metamorphosis of the Liver: Needle Biopsy Investigation in Human Beings, Arch. Int. Med. **86**:671, 1950. Post, J.; Benton, J. G.; Breakstone, R., and Hoffman, J.: The Effects of Diet and Choline on Fatty Infiltration of the Human Liver, Gastroenterology **20**:403, 1952.

55. Cornatzer, W. E., and Cayer, D.: Effects of Lipotropic Factors on Phospholipide Turnover in Plasma of Patients with Cirrhosis of Liver as Indicated by Radioactive Phosphorus, J. Clin. Invest. **29**:542, 1950.

56. Cayer, D., and Cornatzer, W. E.: The Use of Lipotropic Factors in the Treatment of Liver Disease, Gastroenterology **20**:385, 1952.

57. György, P.: Vitamin B_{12}, Folic Acid, and the Lipotropic Agents, In Liver Injury, Transactions of the Ninth-Tenth Conferences, 1950-1951, edited by F. W. Hoffbauer, New York, Josiah Macy, Jr., Foundation, 1950, p. 206.

58. Levine, H.; Gilbert, A. J., and Bodansky, M.: The Pulmonary and Urinary Excretion of Paraldehyde in Normal Dogs and in Dogs with Liver Damage, J. Pharmacol. & Exper. Therap. **69**:316, 1940.

59. Cameron, G. R., and de Saran, G. S. W.: The Effect of Liver Damage on Action of Some Barbiturates, J. Path. & Bact. **48**:49, 1939.

60. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics: A Textbook of Pharmacology, Toxicology and Therapeutics for Physicians and Medical Students, New York, The Macmillan Company, 1941, p. 178.

61. Wintrobe.[13] Berman and others.[14]

anemia may be more apparent than real because of an increase in circulating plasma volume without an accompanying increase in total red cell mass.[62] There are varying reports regarding the mechanism of the macrocytic anemia. Movitt [63] reported on three patients with cirrhosis and long histories of malnutrition, with megaloblastic proliferation in the marrow, but with free hydrochloric acid in the stomach. They responded to B_{12} or liver extract. Usually, however, the bone marrow is of normal or increased cellularity, and the severity of macrocytosis is not necessarily related to the severity of the liver disease.[14] Wintrobe [64] suggests that the macrocytic anemia may be due to a variety of causes, such as inability to store hemopoietic principle, deficient diet, and faulty absorption, but that the defect is not related to pernicious anemia. This fact may well explain the variable responses to B_{12} and liver extract. Huang and Wang have suggested that destruction of blood in an enlarged spleen may be a factor.[65]

Bleeding tendencies from sources other than esophageal varices are commonly noted. Diffuse submucosal hemorrhages may be present in the stomach, possibly related to excessive enzyme activity. Hemorrhages may be due to hypoprothrombinemia, increased capillary fragility, or thrombocytopenia.[14]

COMMENT

A review of the clinical features of 58 cases of liver coma reveals that the symptoms, objective findings, and laboratory studies differ in no way from those in cases of severe liver disease without coma. Similarly, the histologic appearance of the hepatic lesions varies widely and often shows no more cellular damage than that noted in needle biopsy specimens from patients who recover. It is not the purpose of this discussion to speculate upon some of the mechanisms of defective cellular enzyme metabolism that might be responsible for the lapse into coma and subsequent death. On the other hand, it seems wise to attempt to formulate a logical regimen of treatment based on the limited information presently available. An attempt has been made to select all forms of therapy discussed previously that seem to be of real or theoretical value in the management of hepatic coma, as follows:

1. The dangers of inducing bleeding or aspiration pneumonia by tube feedings do not seem real enough to offset the obvious advantages of tube feedings, when nutrition is so important as a therapeutic measure. Such feedings are given by slow constant drip. One of three special mixtures, the choice depending on the total number of calories and sodium content desired, has been used.[66]

62. Bateman, J. C.; Shorr, H. M., and Elgvin, T.: Hypervolemic Anemia in Cirrhosis, J. Clin. Invest. **28**:539, 1949.

63. Movitt, E. R.: Megaloblastic Erythropoiesis in Patients with Cirrhosis of the Liver, Blood **5**:468, 1950.

64. Wintrobe, M. M.: Clinical Hematology, Ed. 3, Philadelphia, Lea & Febiger, 1951, p. 484.

65. Huang, K. W., and Wang, H. W.: Anemia Associated with Cirrhosis of the Liver: Study of 32 Cases, Arch. Int. Med. **84**:958, 1949.

66. Mixture No. 1 has 1,950 calories in 1,300 cc.; protein, 104 gm.; fat, 46 gm.; carbohydrate, 280 gm.; Na, 1,300 mg. Contents are 200 gm. of skimmed-milk powder, 20 gm. of cocoa, 20 gm. of sugar, 1 qt. of whole milk. Mixture No. 2 has 1,850 calories in 1,300 cc.; protein, 88 gm.; fat, 100 mg.; carbohydrate, 150 gm.; Na, 527 mg. Contents are 200 gm. of "lanolac," 20 gm. of cocoa, 20 gm. of sugar, 1 qt. of whole milk. Mixture No. 3 has 1,172 calories in 1,000 cc.; protein, 56 gm.; fat 60 gm.; carbohydrate, 102 gm.; Na, 27 mg. Contents are 200 gm. of "lanolac," 20 gm. of cocoa, 20 gm. of sugar, 1 qt. of water.

2. Intravenously administered glucose has been considered on an empirical basis to be of prime importance in treating hepatic coma. The hazards of water intoxication and electrolyte imbalance have previously been emphasized. When adequate carbohydrate intake is assured by tube feedings, parenteral administration of glucose may be superfluous.

3. When tube feedings cannot be carried out, nutritional requirements representing 100 to 200 gm. of protein and 300 to 400 gm. of carbohydrate may be supplied by parenteral feedings of amino acids and glucose. The concentration of the glucose and the amount of salt will be determined by the total fluid and electrolyte requirements according to general principles followed in the treatment of any disease. Factors in hepatic coma which may influence these principles include urinary output, fever, vomiting, the use of diuretics or paracenteses, and bleeding.

4. Parenteral administration of vitamin supplements (such as betasynplex® with vitamin C,[67] ascorbin B,[68] or "betalak"[69]), which contain several times the daily requirements, may be added to each feeding or each liter of fluid.

5. When the prothrombin time is low or when aureomycin is used, vitamin K should be given parenterally in doses of 72 mg., even though the response may not be gratifying.

6. The administration of aureomycin by stomach tube in doses of 1 gm. daily would seem to offer broad coverage for infections and at the same time play a role in preventing hepatic necrosis. This dosage is considerably lower than that reported as causing fatty infiltration or decreasing nitrogen balance.

7. Intravenous administration of crude liver extract in doses gradually increasing to 20 cc. daily or, more diluted, to 1,000 cc. would seem to be of value. Ordinary crude liver extract prepared for intramuscular administration does not seem to cause any greater incidence of reactions than preparations for intravenous use.

8. Anemia may be corrected by blood transfusions or administration of washed red cells, according to the fluid requirements, output, and cardiac state. Massive doses of vitamin B_{12} may be of value in macrocytic anemia.

9. Whenever possible, ascites should be controlled by low sodium intake (200 to 600 mg. daily) and use of crude liver extract and mercurial diuretics, rather than by paracenteses.

10. The dangers of water intoxication, hyponatremia, and hypokalemia should be avoided by careful control of fluid and electrolyte balance.

REPORT OF CASES

CASE 1.—W. N., a 65-year-old unemployed laborer, was admitted to St. Louis City Hospital on Feb. 8, 1950, because of anorexia, weight loss, and vomiting of several months' duration. Informants stated that he had been a heavy drinker in former years, but that recently he had imbibed less and had been on a fairly adequate diet.

67. Betasynplex® with vitamin C contains ascorbic acid, 500 mg.; thiamine hydrochloride, 300 mg.; riboflavin, 100 mg.; nicotinamide 1,000 mg.; calcium pantothenate, 50 mg.; pyridoxine hydrochloride, 50 mg.

68. Each ampule of ascorbin B contains thiamine hydrochloride, 50 mg.; riboflavin, 10 mg.; nicotinic acid 250 mg.; pyridoxine hydrochloride, 50 mg.; pantothenic acid, 50 mg.; ascorbic acid, 1 gm.

69. Each cubic centimeter of "betalak" (10 cc. per ampule) contains thiamine hydrochloride, 10 mg.; riboflavin, 2 mg.; nicotinic acid, 100 mg.; pyridoxine hydrochloride, 1 mg.; pantothenic acid, 1 mg.; ethanolamide gentisic acid, 25 mg.

Physical examination revealed a poorly nourished, dehydrated, confused, and disoriented man. He was mildly icteric, and his skin had large areas of ecchymoses. The percussion note was impaired, and coarse rales were heard over the right lung base posteriorly. A firm, nontender liver edge was felt extending down to the level of the iliac crest. Ascites was not present.

The red cell count was 3,570,000, the white cell count 8,200, and the hemoglobin content 12.0 gm. Urinalysis revealed a 3+ reaction for albumin, a 2+ reaction for acetone, and no sugar. The cephalin flocculation test was 3+, the thymol turbidity 1.1 units, the serum albumin 3.51 gm. per 100 ml., and the serum globulin 2.49 gm. per 100 ml. The serum bilirubin was 3.6 mg. and the total cholesterol 118 mg. (50% esters) per 100 ml., the blood chlorides 67 mEq. per liter, and the carbon-dioxide-combining power 34.2 mEq. per liter.

The patient was given a high-protein, high-carbohydrate diet, penicillin, vitamin supplements, crude liver extract, and repeated infusions of 5% dextrose in water. His course was progressively downhill, with increasing weakness, lethargy, and finally coma.

On the 16th hospital day an electrocardiogram showed evidence of hypokalemia, and the serum potassium was 2.2 mEq. per liter. The chlorides at this time were 87 mEq per liter; 5% sodium chloride and 2% ammonium chloride with 8 gm. of potassium chloride were administered intravenously daily. The response was immediate, with increasing alertness and clearing of the sensorium. Within five days the patient was walking, and his serum electrolytes were within normal limits.

CASE 2.—K. P., a 31-year-old factory worker, was admitted to the St. Louis City Hospital for the second time on March 20, 1951, because of ankle edema and ascites of four months' duration. He denied alcoholism, but had been exposed to naphthalene in his occupation. Ten years previously he had had an episode of painless jaundice lasting six weeks.

Physical examination revealed a lethargic, somewhat disoriented, young man with a distended abdomen and mild icterus. The abdomen was protuberant and taut, with shifting dullness and a demonstrable fluid wave. There was 4+ ankle edema. The chest and axillary hair were sparse, but no spiders or liver palms were noted.

The urine gave a 2+ reaction for albumin, and the specific gravity was 1.019; microscopic examination of the sediment revealed 8 to 10 white blood cells, numerous red blood cells and an occasional granular cast. Liver studies gave the following results: cephalin-cholesterol flocculation 3+; thymol turbidity 17 units; total serum proteins 6.30 gm., albumin 1.34 gm., globulin 4.96 gm., and cholesterol 125 mg. (76% esters) per 100 ml.; sulfobromophthalein sodium retention at 45 minutes 44%, and serum bilirubin, total 2.6 mg. and direct 0.4 mg. per 100 ml. Blood chemistry studies on admission to the hospital showed a blood urea nitrogen level of 37 mg. per 100 ml.; chlorides 106 mEq. per liter, and carbon-dioxide-combining power 24.3 mEq. per liter.

The patient was given a high-protein, low-salt diet and received intermittent injections of mercaptomerin sodium (thiomerin sodium®), with poor control of the ascites. Six paracenteses were required over a period of nine weeks, the total amount of fluid removed measuring 52,050 cc. He received daily infusions of 5% dextrose in water.

His course was gradually downhill. On May 12, the serum sodium was 133 mEq., potassium 4.1 mEq., carbon dioxide 23 mEq., and chlorides 93 mEq. per liter. On May 15, the serum sodium had fallen to 124 mEq. and the potassium to 3.9 mEq. per liter, and the patient was drowsy. He responded temporarily to 5% sodium chloride intravenously, but soon his jaundice increased and he lapsed into coma. He died May 20.

Postmortem examination revealed postnecrotic nodular cirrhosis.

CASE 3.—N. B., a 59-year-old man, was admitted to the St. Louis City Hospital on March 5, 1951, because of ankle edema and ascites. About six weeks prior to admission his abdomen "began swelling," and two weeks prior to admission a paracentesis was performed. At this time it was noted that there was an icteric tint to the skin. The ascites soon recurred, and the patient was hospitalized for further therapy. The past history revealed that the patient had consumed a half pint of whisky and several bottles of beer daily.

Physical examination revealed an elderly cachetic man appearing chronically ill. The skin was icteric. There was marked abdominal distention, with bulging in the flanks, and a free fluid wave was elicited. The liver and spleen were not palpated. There was 2+ edema of the lower extremities.

The essential laboratory findings were: cephalin-cholesterol flocculation 4+; thymol turbidity 17 units; serum albumin 2.04 gm. and serum globulin 4.26 gm. per 100 ml.; serum sodium 142 mEq. and serum potassium 5.0 mEq. per liter.

The patient was given a 0.5 gm. sodium diet, crude liver extract, thiamine, nicotinic acid, choline, and daily injections of mercaptomerin sodium (thiomerin sodium®). Because of continued weight gain, repeated paracenteses were necessary. On April 23 administration of a cation exchange resin was started, 15 gm. three times daily. Since there was no response the dosage was increased on May 1 to 30 gm. three times daily. On May 2 the patient was found to be disoriented and walking unsteadily. On May 3 the serum potassium was 2.6 mEq. and the serum sodium 138 mEq. per liter. The patient was given 200 cc. of salty broth with 6 gm. of potassium chloride. On the following morning he was somewhat improved, but by noon he had again become disoriented and semicomatose. The serum sodium was 143 mEq. and the serum potassium still 2.6 mEq. per liter. He was given 2.0 gm. of potassium chloride every hour for five doses, and administration of the resin was discontinued. On the following day his sensorium had cleared.

On May 13 a paracentesis was performed, with removal of 12.5 liters of fluid. Two days later the resin therapy was resumed, 30 gm. three times daily. Within 48 hours the patient again became somnolent. The serum sodium was 129 mEq. and the serum potassium 3.3 mEq. per liter. On the following day, after administration of 1,000 cc. of 5% dextrose in saline, the serum sodium was 134 mEq. and the serum potassium 2.3 mEq. per liter. Administration of the cation exchange resin was discontinued, and the patient was given potassium chloride daily. On May 21 the serum sodium was 139 mEq. and the serum potassium 4.2 mEq. per liter. At this time he was alert and mentally clear.

Several months later the patient became comatose again and died.

CLINICAL AND LABORATORY STUDY OF THIRTY-ONE PATIENTS WITH HEMORRHAGIC FEVER

CAPTAIN GIULIO J. BARBERO
CAPTAIN SIDNEY KATZ
LIEUTENANT HENRY KRAUS
AND
COLONEL CHARLES L. LEEDHAM
MEDICAL CORPS, UNITED STATES ARMY

INTRODUCTION

IN THE summer and fall of 1951, an acute febrile illness complicated by hypotension, widespread hemorrhage, and renal insufficiency occurred in epidemic proportions among United Nations troops in Korea. At first, the slight resemblance to Weil's disease suggested that the illness was a form of leptospirosis; however, this possibility was removed as the result of negative serological and dark-field examinations for Leptospira and the absence of any severe hepatic involvement. Craig,[1] Takami,[2] and Mayer[3] in searching the Japanese and Russian literature found that both Japanese and Russians had encountered the same disease periodically since 1935 in Manchuria. The Japanese had labeled it "Manchurian fever" or "Songo fever," and the Russians had descriptively named it "epidemic hemorrhagic nephrosonephritis." Both the Japanese and the Russians claimed to have isolated a tranmissible agent by animal inoculation. They also described a mite as the vector and a field mouse as the host of the disease. Their cases appeared sporadically throughout the year with the greatest number developing in the late spring, summer, and fall. The disease involved principally troops located in the field and frequently those in units associated with horses. The mortality rate was apparently 10 to 15%. Pathologically, their reports described characteristic hemorrhages into the anterior pituitary lobe, the wall of the right atrium, the gastric mucosa, and the renal medulla and pelvis. No specific therapy was found, although convalescent serum was stated to be of some value. There was considerable variation in the observations of these workers, as well as lack of a careful clinical study of a large group of patients. In view of the increased importance of this disease and unfamiliarity with it of American physicians, the present study was undertaken.

This study was carried on at the 21st Evacuation Hospital, Pusan, Korea.

1. Craig, J. P.: Epidemic Hemorrhagic Fever, 406 Medical General Laboratory Report, February, 1951.

2. Takami, R. M.: Epidemic Hemorrhagic Fever, Report of the Medical Section, General Headquarters, Far East Command, August 13, 1951.

3. Mayer, C. F.: Epidemic Hemorrhagic Fever, Armed Forces Medical Library Report, 1951.

CLINICAL MATERIAL AND METHODS

Thirty-one patients, ranging in age from 18 to 28, were hospitalized between the second and ninth days of their illness with the average on the fifth day. On admission, each patient was weighed, and 24-hour fluid intake and output measurements were initiated. An electrocardiogram was made and a lumbar puncture performed soon after admission. Routine laboratory studies, including urinalysis, blood cell counts, and determination of the hemoglobin, sedimentation rate, blood nonprotein nitrogen, blood creatinine, serum chloride, and carbon dioxide-combining power of the blood, were made daily until each value returned to normal. Bleeding time, capillary fragility, platelet count, and clotting time were measured daily during the acute and early convalescent periods of the disease. After the acute stage of the illness, liver and kidney function studies were performed. These included determination of the total serum protein and the albumin-globulin ratio, cephalin-cholesterol flocculation, thymol turbidity test, 5 mg.-per-kilogram sulfobromophthalein sodium (bromsulfalein sodium®) test, 12-hour urine concentration test, Volhard-Fahr dilution test, and 15-minute intravenous phenolsulfonphthalein-excretion test.

A clinical estimate of the severity of illness was made in each case and was arbitrarily based on the collective severity of certain common signs and symptoms. A scale of 1+ to 4+ being used, the over-all clinical severity was based on pain, malaise, weakness, gastrointestinal symptoms, restlessness, somnolence, bleeding phenomena, oliguria or anuria, shock, neurological complications, and hiccoughs. The 31 patients were divided into four classes according to severity of illness, as follows: 1+, 12 patients; 2+, 11 patients; 3+, 3 patients; 4+, 5 patients.

EPIDEMIOLOGY

From November, 1951, to March, 1952, 1 English and 30 United States front-line troops between the ages of 18 and 28 were studied. Of these, 27 men were assigned to the 1st Cavalry, to the 3d or the 25th Division, or to attached 8th Army units, while the remaining 4 men were assigned to the 2d, the 7th, or the Commonwealth Division. Chart 1 indicates the geographical distribution of these cases of hemorrhagic fever. The greatest concentration of cases occurred in or near the cities of Kumhwa, Chorwon, and Yonchon, Korea. The men came from infantry, field artillery, tank, headquarters, engineering, and reconnaissance units. Individual assignments included rifleman, gunner, cook, tank driver, truck driver, ammunition bearer, road-labor boss, switchboard operator, gate guard, medical-aid man, rodent-control man, clerk, and digger of garbage pits. Rats, mice, or both were numerous in their surroundings, and frequent evidence of rodents was present in food and clothes. Living quarters consisted of bunkers or tents. Only government-issued food and water were ingested. The onset of illness was between Oct. 30, 1951, and Jan. 10, 1952. The men were in their respective sites in Korea for periods of 2 to 20 weeks before the onset. One patient became ill 13 days after leaving an epidemic area.

DATA FROM CLINICAL STUDIES

Onset.—The first symptom of disease in 77% of the patients was either headache, chills, or fever. Other symptoms of onset included malaise, fatigue, anorexia, backache, eye pain, dizziness, myalgia, and arthralgia. In 64% of the cases, the onset was gradual over a period of 12 to 48 hours. In 36% of the cases, the onset was abrupt, usually starting with chills and fever. The onset was preceded by symptoms of a developing cold in three patients.

Fever (Chart 2).—All patients had fever. The temperature course could be divided into three periods, a phase of acute elevation, a secondary phase of low-grade elevation, and a convalescent phase of normal temperature. The duration of the

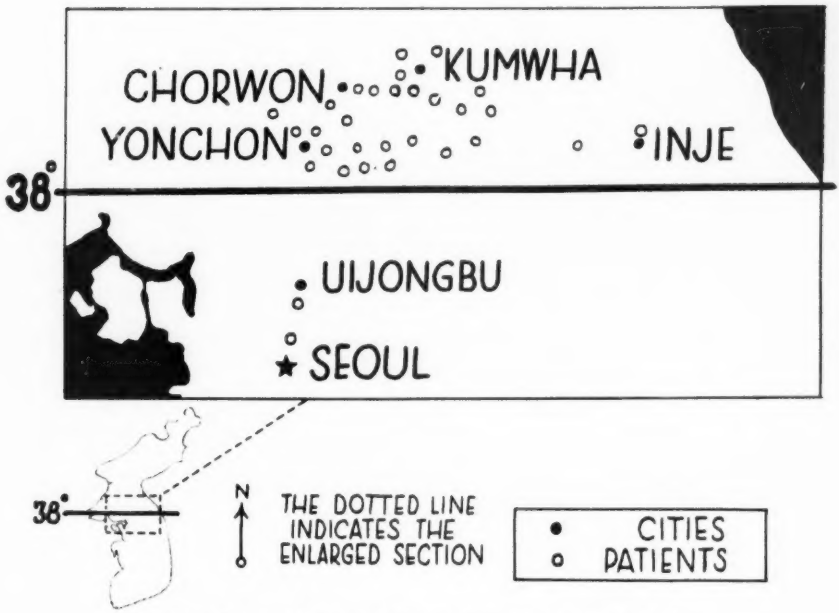


Chart 1.—Geographical distribution of 31 cases of hemorrhagic fever.

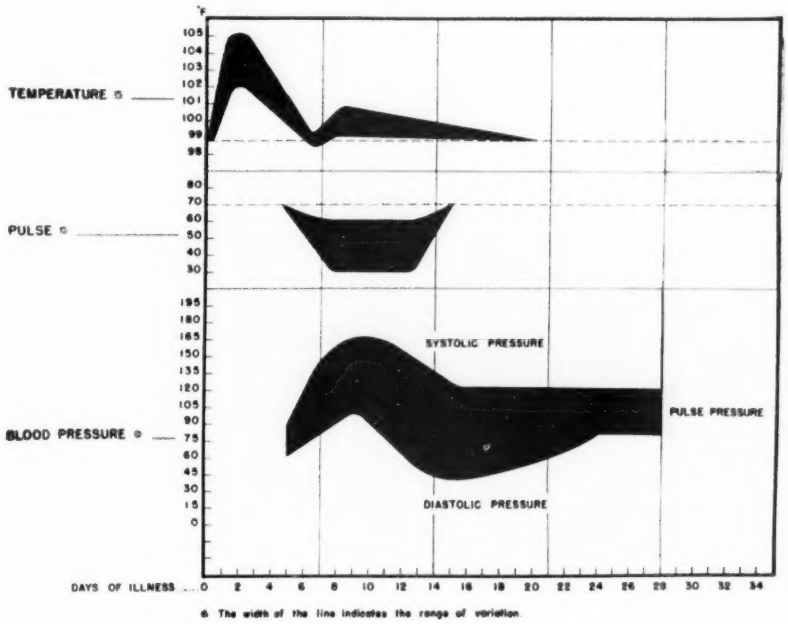


Chart 2.—Fever, bradycardia, and blood pressure in 31 cases of hemorrhagic fever.

phase of acute elevation averaged 6 days, ranging from 3 to 10 days, and was not correlated with severity of illness. During this phase, all temperatures were elevated, and 83% were above 100 F. Of the maximum temperatures recorded, 96% were between 102 and 105 F. The peak temperatures occurred within the first six days of illness. There was no direct correlation between the height of temperature and the severity of illness, although two of the highest temperatures (105 F.) occurred in the two most critically ill patients.

The duration of the secondary febrile phase averaged 14 days, ranging from 4 to 39 days. Of the maximum temperatures recorded in this phase, 93% were between 98.8 F. and 100.6 F., and in 18 patients the peak occurred within the first three days of the phase. In general, the secondary phase was longer than two weeks

TABLE 1.—*Clinical Symptoms of Thirty-One Patients with Hemorrhagic Fever*

Symptom	No. of Patients	%	Day of Onset	Duration (Days)	
				Range	Average
Malaise	31	100	1	2-22	9
Anorexia	31	100	1-3	2-16	9
Thirst	30	97	1-2	4-23	11
Fatigue	30	97	1	4-36	10
Headache	30	97	1-2	1-22	7
Insomnia	30	97	1	2-15	7
Chills	30	97	1-2	1-7	4
Backache	27	87	1-3	1-18	7
Abdominal pain	27	87	1-6	1-15	6
Dizziness	26	84	1-3	1-8	4
Nausea	24	77	1-5	1-25	6
Vomiting	24	77	1-6	1-14	5
Cough	24	77	1-5	1-14	5
Diaphoresis	22	71	1-5	1-10	5
Eye pain	19	61	1-4	1-21	5
Blurred vision	19	61	1-5	1-9	3
Coryza	17	55	1-6	1-11	5
Myalgia	17	55	1-3	1-11	4
Painful swallowing	11	36	1-6	1-8	5
Stiff neck	9	29	1-5	1-9	5
Sore throat	7	23	1	2-8	6
Arthralgia	7	23	1	1-6	4
Diarrhea	5	16	1-7	1	1
Palpitation	3	10	1	5-6	6

in the more severely ill patients and shorter than two weeks in the less severely ill. By arbitrary definition, the convalescent phase began when the temperature returned to normal, at which time certain laboratory findings and physical signs were still abnormal.

Table 1 summarizes the frequency, day of onset, and duration of symptoms. Shaking chills or chilly sensations were of short duration and occurred during the acute febrile phase in 97% of the patients. Thirst was marked in 97% of the patients, starting at the time of chills and fever and lasting into the second week. Mild diaphoresis accompanied the acute febrile phase.

All patients had malaise on the first day of illness. It was severe and subsided gradually within two weeks. Fatigue followed a similar course, often lasting a few days longer. Insomnia with night restlessness varied from mild to severe, started on the first night of illness, and lasted one to five nights. Most commonly, headache appeared within the first two days of illness and disappeared in about one week.

Headache was severe, described as "dull," "pressure," or "ache." It was frontal in 77% of the patients, almost always periorbital, and of "hours" to "constant" duration. One-fourth of the patients with frontal headache had associated occipital headache, and individual instances occurred of headache referred to any part of the cranium. Dizziness and eye pain occurred in 84% and 61% of the patients, respectively. Dizziness was mild and occurred chiefly on standing or changing position. Eye pain was manifested as either pain on motion or "pressure" pain and occurred during the acute febrile phase. It was often associated with burning, photophobia, or blurred vision. In general, the more severely ill patients had more prolonged malaise, fatigue, insomnia, headache, and thirst.

Backache and muscle and joint symptoms appeared at the onset of the acute febrile phase. Backache occurred in 87% of the patients. It was severe and of two general types, high costovertebral-angle pain and low lumbosacral pain, the latter probably muscular. Mild to moderate myalgia other than backache was a symptom in about half of the patients. This involved the calves and thighs most commonly and secondly the arms, neck, shoulders, and chest. There was nuchal rigidity in 29% of the patients. It was associated with either central nervous system lesions or cervical muscle pain. On admission, 97% of the patients complained of weakness. One-fifth of the patients had mild arthralgia, which involved the knees, hips, shoulders, and elbows in that order of frequency. There was no direct correlation between severity of illness and severity or duration of backache, myalgia, arthralgia, or nuchal rigidity.

About half of the patients complained of symptoms of a "cold," including slight nasal discharge, nasal congestion, cough, and sore throat. Mild, nonproductive cough was present in 77% of the patients during the first week. Epistaxis and hemoptysis were not uncommon and occurred during the period of hemorrhagic phenomena. Infrequently, symptoms of mild exertional dyspnea and palpitation were encountered.

All patients had anorexia. Usually it was severe, started on the first day of illness, subsided in less than two weeks, and was accompanied by nausea and vomiting. Nausea and vomiting occurred in 77% of the patients and lasted about one week. Anorexia and lack of eating were associated with lack of bowel movements in one-third of the patients. This was rarely a cause for complaint. Transient, mild diarrhea during the first week of illness was described by five patients. Abdominal pain was a symptom in 87% of the patients. There was an equal incidence of periumbilical, upper abdominal, and lower abdominal pain, and two patients had generalized abdominal pain. Decreased micturition was described by one-third of the patients and a questionable decrease by an additional 16%. One patient was anuric when admitted. Anorexia, nausea, vomiting, and abdominal pain were generally more prolonged in patients who were more severely ill.

Table 2 summarizes the frequency of clinical signs. On admission, 42% of the patients were markedly restless, and three severely ill patients were somnolent. Skin examination revealed facial flush in 90% of the patients, with the greatest intensity over the cheeks, forehead, and upper eyelids. The flush involved the neck in half of the patients and occasionally involved the upper chest. It averaged one week in duration. Dermographism was present in 94% of the patients, at the same time as the flush. Multiple pruritic papules were observed on the medial aspects of the thighs of one patient. No parasites were found, and the lesions disappeared spon-

taneously in two days. "Dime-sized," erythematous skin lesions were claimed by one patient, but these were not found upon examination. The remaining patients had no rashes.

Severe vascular injection of the palpebral conjunctiva was present in 90% of the patients. In half of these, bulbar conjunctival injection was also present, but less prominent. Snellen and Jaeger standard eye charts were used to follow daily visual acuity in 12 patients. In two of these, vision was 20/200 in each eye, Jaeger 10, and 20/50 in each eye, Jaeger 2, on admission, improving to 20/20 in each eye, Jaeger 1, in two and five days, respectively. A similar but lesser degree of change was observed in five patients, while the remaining five showed no significant change.

Four-fifths of the patients had vascular injection of the oral, pharyngeal, and nasal mucous membranes. Pharyngeal exudate was not present. A few patients

TABLE 2.—*Clinical Signs in Thirty-One Pateints with Hemorrhagic Fever*

Sign	No. of Patients	%
Fever	31	100
Bradycardia	30	97
Costovertebral-angle tenderness	30	97
Dermographism	29	94
Conjunctival injection	28	90
Facial flush	28	90
Abdominal tenderness	27	87
Evidences of bleeding	27	87
"Coated" tongue	27	87
Facial and periorbital edema	25	81
Mucous membrane injection	25	81
Conjunctival edema	22	71
Abdominal distention	16	52
Hiccoughs	14	45
Restlessness	13	42
Hepatomegaly	13	42
Nuchal rigidity	8	26
Neurological complications	5	16
Somnolence	3	10
Muscle tenderness	3	10
Splenomegaly	1	3

complained of pain on swallowing despite normal appearance of the pharynx. "Coating" of the tongue was observed in 87% of the patients. Facial, periorbital, and conjunctival edema occurred in 81%, 81%, and 71% of the patients, respectively, for three to five days. There was only general correlation between severity of illness and duration of flush, dermographism, mucous membrane injection, and edema.

The chest, lung, and heart examinations gave normal results except in one patient with a few transitory, coarse basal lung rales and three patients with heart sounds of poor quality. These signs disappeared within one or two days. The abdomen was tender to deep palpation, without rigidity, in 87% of the patients. The tenderness was localized in all but two critically ill patients, in whom it was generalized. Distention accompanied tenderness in half of the patients. Hiccough occurred in about half of the patients, and its severity was correlated with the amount of edema present. In more than one-third of the patients the liver was slightly tender, smooth, and enlarged for two days after admission. In one patient, the spleen was enlarged and tender on admission and became normal in two days. Almost all patients had generalized lymphadenopathy. The lymph nodes were usually not

tender. Unilateral or bilateral costovertebral-angle tenderness was present in all but one patient. There was only general correlation between severity of illness and the duration of abdominal and costovertebral-angle tenderness.

Hemorrhagic Phenomena.—At least one sign and/or symptom of bleeding was noted in 87% of the patients. Details of site and incidence of bleeding are given in Table 3. The duration of bleeding phenomena ranged from one to nine days, averaging three days. It was associated with the interval of low platelet count.

Epistaxis occurred in 42% of the patients. It was generally mild and of short duration, lasting one to three days. In two patients, it was severe, persisting for three and six days, respectively. Hemoptysis was mild, occurring in five patients for one to two days. Hematemesis was observed in seven patients. Its duration averaged four days, ranging from two to seven days. Melena appeared in three patients for an average duration of one day. One-fourth of the patients had ecchy-

TABLE 3.—*Site of Hemorrhage in Thirty-One Patients with Hemorrhagic Fever*

Site	No. of Patients	%
Genitourinary tract	31	100
Gastrointestinal tract		
Oropharynx, petechiae	17	55
Hematemesis	7	23
Melena	3	10
Respiratory tract		
Nasal mucosa, petechiae	6	19
Epistaxis	13	42
Hemoptysis	5	16
Eye		
Conjunctiva and sclera	13	42
Retina	2	6
Skin		
Petechiae	12	39
Ecchymoses	8	26
Subarachnoid space	4	13
Tympanic membrane	1	3

moses, initiated by trauma and appearing most frequently at the sites of needle punctures. Skin petechiae were noted in one-third of the patients, appearing at pressure areas, including the axillary folds, belt line, flanks, hips, thighs, and lateral chest walls. The distribution corresponded largely with those sites which were traumatized by lifting and moving the patients during the period of evacuation. One-half the patients had petechiae of the oropharynx, which involved in order of frequency the soft palate, tonsillar pillars, buccal mucosa, posterior pharyngeal wall, and uvula. The buccal mucosa was usually involved at the line of closure of the teeth. In one patient, petechiae of the palate involved denture-pressure areas. Subconjunctival hemorrhages appeared in 42% of the patients. They were associated with severe or prolonged vomiting and conjunctival edema. Retinal hemorrhages occurred in two patients, both of whom had severe vomiting. A large hemorrhage of the eardrum occurred in one patient. The spinal fluid was grossly bloody in four patients, and in three of these, there was evidence of neurological involvement.

Neurological Changes.—Abnormal neurological signs were present in five patients. In a four-day hospital course, the one patient who died manifested restlessness, uninhibited speech, somatic delusions, tremors, muscle incoordination,

twitching, and a generalized convulsion. This patient also had a retinal hemorrhage, elevated spinal fluid pressure, and xanthochromic spinal fluid. Severe uremia was present during this period. The second patient on admission had a positive Kernig sign, stiff neck, absence of abdominal reflexes, and absence of the left cremasteric reflex. The spinal fluid protein was elevated. He was somnolent for six days, but later recovered without neurological sequelae.

The third patient had a depressed sensorium, diminished reflexes, and decreased motor power on admission. The next day, he became restless. Two days later, he had a stiff neck, stiff back, positive Kernig sign, and grossly bloody spinal fluid. Improvement occurred in the following nine days, at the end of which time the spinal fluid was clear yellow. This patient had no neurological sequelae. In the fourth patient there developed thigh and low back pain, incontinence, muscle weakness, and anesthesia of the lower extremities, bilateral absence of knee and ankle jerks, stiff neck, stiff back, and a patulous rectal sphincter. The spinal fluid was grossly bloody, and a retinal hemorrhage developed. Over a three-month period of observation, urinary and fecal continence reappeared, reflexes and sensation returned, and muscle strength gradually improved, but a foot drop on the left persisted. The fifth patient was admitted in shock with Cheyne-Stokes respiration and severe uremia. He had diminished reflexes and restlessness. During the next three days of severe oliguria, muscle twitching, a generalized convulsion, a positive Babinski sign, and sustained ankle clonus developed. After the diuretic period, he became somnolent. His improvement was slow, but he recovered without neurological sequelae.

Cardiovascular Changes (Chart 2).—Between the 5th and 19th days of illness, 29 patients had periods of relative bradycardia, averaging 6 days a patient. This was defined as a period during which a significant number of pulse rates were low for the corresponding temperatures and low when compared with pulse norms. During this period, among 28 patients a significant number had pulse rates of less than 60 beats a minute. The average fall in pulse rate was about 20 beats a minute. There was no correlation between severity of illness and duration or severity of bradycardia. In two patients, there were three-day intervals of tachycardia between the second and fifth days of illness. The two most critically ill patients had periods of tachycardia during the second week of illness. One of these was admitted without perceptible pulse or blood pressure and had tachycardia upon being brought out of shock. The other patient was admitted with a tachycardia which persisted for three days, until he died. The remaining 27 patients had no significant tachycardia; however, no conclusions could be drawn concerning the heart rates early in the disease, since 84% of the patients were admitted on the fifth day of illness or later, and pulse rates were not generally observed before this.

Abnormally high and low systolic, diastolic, and pulse pressures were observed. On admission, systolic pressures were low or normal, increasing to levels above normal on the 3d to 11th day of illness. Diastolic pressures almost paralleled this rise, being elevated on the 4th to 13th day of illness (period of oliguria). Abnormally low diastolic pressures occurred after the oliguric phase in the second week, and occasional low values were noted for several weeks thereafter. Pulse pressures were narrow or normal on admission, remaining thus or decreasing for two to three days. In 21 patients, wide pulse pressures appeared one to five days after the narrow pulse pressures and often continued into the afebrile phase for one to two weeks.

Instability of blood pressure was indicated by the fact that abnormally high and low pressures occurred sporadically throughout the disease in all patients. Patients who were more severely ill had more severe hypotensive and hypertensive episodes.

Water Balance and Renal Aspects.—Chart 3 shows the relationships between the water balance and renal aspects of the disease. The signs associated with renal disease included oliguria, anuria, edema, costovertebral-angle tenderness, and uremic manifestations. These signs of renal involvement became most severe near the end of the first week of illness and persisted for about seven days.

Urine Output.—In 50% of the patients, a progressive fall in urine output began during the first week of the disease and continued for two to seven days. In these

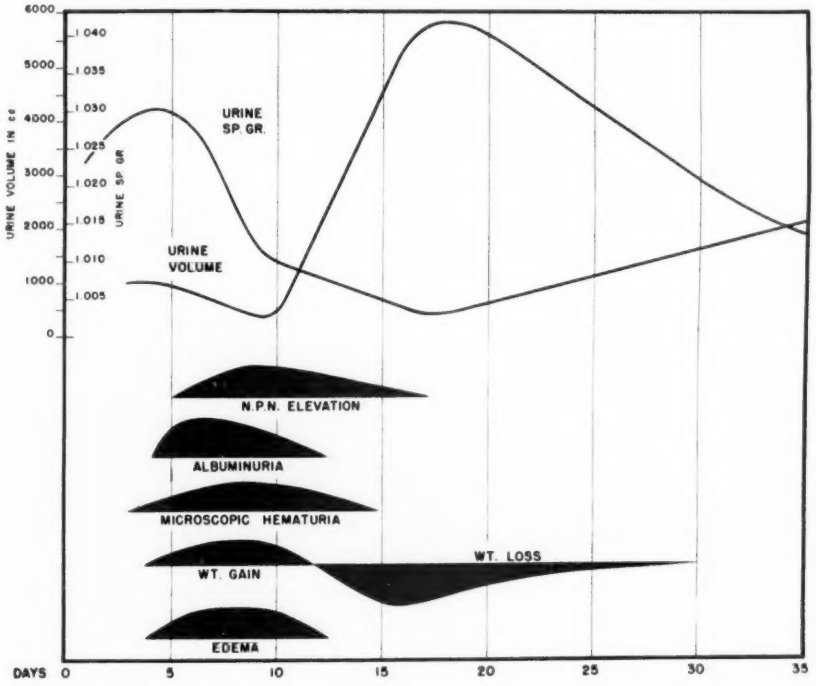


Chart 3.—Correlation of water balance, urinary findings, and blood nonprotein nitrogen in 31 cases of hemorrhagic fever.

patients, the urine volumes fell to levels below 800 cc. a day. Urine volumes of less than 300 cc. a day were seen in 20% of the patients, one of whom was completely anuric for four days. The lowest urine volumes occurred between the 4th and 10th days of illness (8th day average). One patient died during the period of oliguria, and in the others gradual increases in urine volume developed between the 5th and 12th days. The urine volumes rose above 2,500 cc. a day in all patients and above 4,500 cc. in 58% of them, with occasional volumes above 6,000 cc. a day during this diuretic period. Peak outputs were reached between the 7th and 26th days (12th day average). The high urine outputs were due to the loss of renal concentrating ability which occurred in the first week of the disease.

Fluid Intake and Water Balance.—Water balance was determined by subtracting the urine output plus 700 cc. (insensible fluid loss) from the total intake.

In 11 patients, intake and output were measured early enough in the course of the disease to establish a characteristic pattern. A positive water balance occurred in the 1st week of the disease and continued up to about the 8th day (range of 4th to 12th day), when a spontaneous diuresis and resultant negative water balance occurred. The early positive water balance coincided in time with the development of facial and periorbital edema and the period of oliguria. This was a critical period in the management of the patients, for excessive administration of fluids during this time might have precipitated pulmonary edema. With the appearance of polyuria and a negative water balance, the danger of excessive fluid administration rapidly diminished.

Weight.—An early weight gain was noted in 16 patients, its peak occurring between the 3d and 13th days of illness (9th day average). This increase in weight coincided with the end of the oliguric period and the time of positive water balance. The average weight gain was 2.5 lb. (1.1 kg.) with a range of 1 to 7 lb. (0.5 to 3.2 kg.). Even a 1-lb. rise was considered significant, because of the poor food intake, vomiting, and catabolic effects of disease which occurred during this period. A subsequent weight decrease appeared in all patients as the result of loss of both edema fluid and protoplasmic substance. The lowest weights were recorded between the 5th and 26th days of the disease (15th day average). The average weight loss was 6 lb. (2.7 kg.) (range of 0.5 to 7.3 kg.), and 57% of the patients lost more than 5 lb. (2.3 kg.). Weights returned to the admission levels between the 8th and 80th days of the disease.

DATA FROM LABORATORY STUDIES

Hemoglobin.—The hemoglobin level was increased to an average of 17.5 gm. in 25 patients about the sixth day of illness. This hemoglobin elevation paralleled the fever and vomiting, suggesting its relationship to dehydration. There was a fall in the hemoglobin level with cessation of vomiting in these patients. The six patients without elevation of hemoglobin did not vomit. A second hemoglobin elevation to 16.5 gm. appeared in 20 patients at the end of the second week. This second hemoglobin rise occurred at the same time as the peak of the diuresis, suggesting hemoconcentration. The hemoglobin level was diminished to 10 gm. in one patient who had marked intestinal bleeding.

Red Blood Cells.—The red blood cell count rose to an average of 6,500,000 per cubic centimeter in 60% of the patients at the end of the first week and returned to a normal level in the second week of the disease. This increase in the red blood cell count paralleled the hemoglobin rise and also reflected the degree of hemoconcentration. During the convalescent period, the red blood cell count was stabilized at an average level of 4,700,000 per cubic centimeter.

Hematocrit Reading.—The hematocrit reading was increased to an average of 54 mm. in 75% of the patients about the sixth day of illness and returned to a normal level by the eighth day. The increase was well correlated with vomiting in 75% of the patients and paralleled a similar rise in the hemoglobin and red blood cell count. In 15 patients, the hematocrit value dropped further, to an average of 37.5 mm., on the 9th and 10th days of the disease. The drop occurred at the same time as the maximum weight gain and the end of the oliguric period. On about the

11th day of illness, there was a second rise in 18 patients. The concurrent increase in the hematocrit reading and hemoglobin content at this time probably reflected a rapid loss of plasma water due to the marked diuresis.

White Blood Cells.—The white blood cell counts were elevated to 10,000 to 56,000 per cubic millimeter in 28 patients between the fifth and ninth days of illness (seventh day average). The distribution of the elevated white blood cell counts is shown in Table 4. The average white cell count fell below 10,000 on the 13th day (range of 8th to 20th day). In 95% of the patients, a second rise, of between 10,000 and 20,000 cells, appeared at the end of the second week and the count fell below 10,000 in the third week of the disease. This elevation occurred at the same time as the second increase in hemoglobin value and hematocrit reading. In five of eight patients admitted prior to the fourth day of illness, the white cell counts ranged between 3,600 and 6,000. Although the highest counts were found in the severely ill patients, the number of white cells generally showed no correlation with the severity of illness.

Differential Blood Smears.—The serial examination of the blood smears of 30 patients revealed a consistent and characteristic blood cell picture in this disease. In the first week of illness, there was a marked shift to the left in the neutrophilic series,

TABLE 4.—*White Blood Cell Counts for Thirty-One Patients with Hemorrhagic Fever*

White Blood Cells per Cu. Mm.	No. of Patients	%
Below 10,000	3	10
10,000-20,000	17	55
21,000-30,000	8	25
31,000-56,000	3	10

with the appearance of myelocytes, metamyelocytes, stab forms, and occasional promyelocytes in the peripheral blood. These cells comprised a maximum of 90% or more of the differential count at the time of the greatest leucocytosis. From the second week to the convalescent period, the young granulocytic cells disappeared from the peripheral blood and were replaced by a rising percentage of cells of the mononuclear series. In several patients, the leukemoid shift completely changed to a mononuclear picture within 24 hours. All neutrophiles showed toxic degeneration and granulation.

The lymphocytic series included many atypical forms, which were predominantly of the Downey No. 1 and 2 variety. These cells appeared in small numbers during the first week of illness, when the leukemoid shift was the most prominent. The percentage of abnormal and normal lymphocytes gradually rose to as much as 60% of the differential count in the third to sixth week of illness. High lymphocyte percentages persisted for as long as three months.

Monocytes were rare or absent in the first week of illness. From the second to fourth week, they increased to as much as 15% of the differential count. The monocytes were immature and abnormal in appearance. Some of these cells resembled promonocytes, and others were large, with a more deeply basophilic nucleus and more compact chromatin. The cytoplasm was darker than that of normal monocytes and often finely stippled. Many forms seemed to bridge the gap between the lymphocytic and monocytic series. The nucleus was often folded, presenting an appearance similar to that of a large polymorphonuclear leucocyte.

Eosinophiles were rare or absent in the first week of illness. In 73% of the patients, there was a gradual increase in eosinophiles to a maximum level of 5% to 19% in the third week of illness. The eosinophiles returned to normal levels by the fourth week.

Basophiles were absent or diminished in number in the acute febrile phase. During the third week of illness, they reached levels of 3% to 5% of the differential counts.

Thrombocytes were rare in the peripheral blood at the end of the first week of illness. Their absence was correlated with the depression of the thrombocyte count by the direct counting method. In the admission blood smears of all patients, macrothrombocytes occurred in a range of 1 to 10 per 100 cells counted. The macrothrombocytes were often as large as red cells, and they disappeared from the peripheral blood smears in the fourth week of illness.

Urine Specific Gravity.—Early in the disease, concentrated urines were noted with specific gravities as high as 1.032 to 1.035. The degree of concentration paralleled such factors as fever and vomiting, and was thus related to dehydration. Between the 3d and 13th days, the specific gravity declined from levels of 1.020 or higher to levels around 1.010. This decline was gradual in 77% of the cases and occurred over an average interval of eight days. In the other 23%, the specific gravity fell within 24 to 48 hours. The rate of fall had no relation to the severity of disease. The specific gravity remained at or below isosthenuric levels for varying intervals between the 8th and 52d days, and there was a good correlation between the severity of the disease and the interval during which the specific gravity remained below 1.012. At some time between the 7th and 25th days (11th day average), the urine became very dilute, with gravities as low as 1.002 (average of 1.005). There was no correlation between the severity of the disease and the lowest level to which the specific gravity fell.

In all cases, the specific gravity gradually returned toward normal during convalescence. The rate of improvement was measured by 12-hour urine concentration tests at weekly intervals, and the number of days required for the specific gravity to reach the arbitrary levels of 1.015, 1.020, and 1.025 offered an index to the rate of improvement. In 30 patients, the specific gravity returned to 1.015 between the 11th and 63d days (23d day average) and to 1.020 betwen the 16th and 93d days (36th day average). Because of the needlessly prolonged hospitalization required for this study, only 18 patients remained long enough for their specific gravities to reach 1.025. In these patients, the range was from the 19th to 129th day (52d day average). There was general correlation between the clinical severity of the disease and the length of time required for the renal concentrating ability to recover fully. It was obvious that the degree of renal damage did not always parallel the severity of the other manifestations of the disease.

Observations were made on the relationship between 24-hour urine volumes and urine specific gravities. During the oliguric period (fourth to eighth day), the specific gravities gradually fell to isosthenuric levels. In the mildest cases, in which no oliguria occurred, the declining specific gravities were actually associated with increasing urine volumes. The low specific gravities during the period of oliguria indicated diminished renal concentrating ability and simultaneous diminished glomerular filtration. Polyuria occurred in all of the patients, starting some time before the end of the second week of illness. The large urine volumes were invariably

associated with low specific gravities, and the lowest specific gravities coincided with the highest urine outputs. Specific gravities progressively rose to isosthenuric levels as the urine volume declined toward normal. The very dilute urines which occurred at the time of polyuria indicated good renal diluting ability relatively early in the course of the disease.

Dilution Tests.—During convalescence, the dilution test of Volhard and Fahr was performed on 24 patients at weekly intervals. This test was started on or before the sixth week of the disease, and the result was normal in 92% of the patients at the time of the first test. In two patients, repeated dilution tests were abnormal for as long as five weeks. There was some reluctance to attribute the abnormal results in these cases to impaired renal function, for in both patients normal phenolsulfonphthalein excretion and only slightly impaired concentrating ability were demonstrated during the period of markedly impaired diluting function.

Albuminuria.—Albuminuria was present in all 31 patients. It first appeared between the 2d and 5th days of illness (4th day average) and disappeared between the 8th and 19th days (11th day average), with an average duration of 8 days

TABLE 5.—*Urine Sediment in Thirty-One Patients with Hemorrhagic Fever*

Formed Element	No. of Patients	Maximum No.		Day of Maximum		Day of Appearance		Day of Disappearance		Duration, Days	
		Average	Range	Average	Range	Average	Range	Average	Range	Average	Range
White blood cells	29	17*	5-50*	8	6-32	8	3-21	21	9-44	13	1-40
Red blood cells	31	18*	1-55*	10	2-29	6	2-10	18	2-50	12	1-48
Epithelial cells	29	13*	5-26*	10	4-18	8	2-15	11	7-26	9	1-18
Hyaline casts	27	6†	1-15†	9	6-20	8	4-13	21	8-66	13	1-43
WBC casts	25	4†	1-10†	11	5-17	9	4-17	12	6-19	4	1-13
RBC casts	19	3†	1-10†	10	6-25	10	6-25	12	6-20	2	1-5
Granular casts	27	5†	1-14†	9	5-21	8	4-21	12	8-21	5	1-15

* Number per high-power field.
† Number per 6 high-power fields.

(range of 1 to 12 days). In five patients, recurrent albuminuria developed later in the disease. It was not persistent, and albumin appeared only in small quantities. There was no correlation between the severity of the disease and the day of onset or the duration of albuminuria, nor was there any relationship between the duration of albuminuria and the length of time that renal concentrating ability remained diminished. There was fair correlation between the quantity of albumin in the urine and the severity of renal disease. The end of albuminuria heralded the onset of improvement in renal findings. A spontaneous diuresis appeared about that time, with a subsequent drop in the blood nonprotein nitrogen and creatinine and subsidence of the uremic state. The end of albuminuria, also, coincided in time with the lowest specific gravities.

Formed Elements of the Urine.—Table 5 summarizes the observations on the urinary sediment. All patients had microscopic hematuria, and in 29 of them, it was present at the time of the first urinalyses, which were performed between the second and 10th days of the disease (6th day average). Microscopic hematuria was present on the third day in four patients who were admitted early enough to have urinalyses performed at that time. The red blood cells persisted in the urine for an average of 12 days, with a wide range of 1 to 48 days. In a few cases, occasional red

blood cells were encountered later in the disease but were not persistent. The number of red cells in the urine varied widely during the course of the disease. The peak of red cell excretion occurred between the 2d and 29th days (10th day average), and the maximum number of cells varied from 1 to more than 55 per high-power field, with an average of 18. Gross hematuria occurred in 1 of the 31 patients and was present between the 9th and 12th days. This patient died on the 12th day.

The presence of more than five white blood cells per high-power field was considered abnormal. This abnormality was observed in 94% of the patients and first appeared between the 3d and 21st days (8th day average), persisting for an average of 13 days (range of 1 to 40 days). The number of white cells reached a peak of 5 to 50 per high-power field (average of 17) between the 6th and 32d days of illness (8th day average).

Epithelial cells appeared in the urine in increased numbers during the early part of the disease. More than 5 epithelial cells per high-power field was considered abnormal. They were first observed between the 2d and 15th days (8th day average) and persisted for an average period of 9 days (range of 1 to 18 days). The maximum epithelial cell excretion occurred between the 4th and 18th days (10th day average), at which time the number of cells varied between 5 and 26 (average of 13).

Urinary casts were divided into the usual groups, including hyaline, white blood cells, red blood cells, and granular types. The number of casts was expressed as the number seen in six high-power fields. Hyaline casts were seen in the urine of 27 of the 31 patients. They appeared between the 4th and 13th days (8th day average) and were present for an average of 13 days (range of 1 to 43 days). The maximum number of hyaline casts varied from 1 to 15 (average of 6) and occurred between the 6th and 20th days (9th day average). Granular casts were observed in the urine of 27 patients. These casts appeared in the urine between the 4th and 21st days (8th day average) and persisted for an average duration of 5 days (range of 1 to 15 days). The maximum number of 1 to 14 granular casts (average of 5) occurred betwen the 5th and 21st days (9th day average). Red blood cell casts were seen in 61% of the cases. They appeared between the 6th and 25th days (10th day average) and persisted for an average period of 2 days (range of 1 to 5 days). The maximum varied between 1 and 10 casts (average of 3) and occurred between the 6th and 25th days of the disease (10th day average). White blood cell casts were present in 81% of the cases and were first observed between the 4th and 17th days (9th day average). They remained for an average of 4 days (range of 1 to 13 days) with a maximum of 1 to 10 white blood cell casts (average of 4) between the 5th and 17th days (11th day average).

In summary, red blood cells were the first abnormal elements seen in the urine, occurring in some cases as early as the third day. They were of considerable diagnostic value early in the disease. The other formed elements appeared about the 8th day of the disease and reached a peak between the 8th and 11th days. This peak corresponded in time to the end of albuminuria, the onset of the diuresis, and the highest levels of nonprotein nitrogen and creatinine.

Blood Nonprotein Nitrogen and Creatinine.—Table 6 summarizes the observations on the nonprotein nitrogen and creatinine. By the end of the first week, 90% of the patients had elevations of blood nonprotein nitrogen, and at the end of eight days, 87% of the patients had elevations of blood creatinine. The maximum level for each occurred at approximately the same time, between the 4th and 14th days

(9th day average for each). The highest nonprotein nitrogen values ranged from 44 to 242 mg. per 100 ml., and the highest values for creatinine were between 1.9 and 16.0 mg. per 100 ml. The values for blood nonprotein nitrogen returned to normal by the 11th to 28th day (17th day average) and the creatinine values by the 6th to 21st day (10th day average). As a group, the more severely ill patients had higher nonprotein nitrogen and creatinine levels than those that were less severely ill. There was, however, no direct correlation between the clinical severity of illness and the maximum levels to which the nonprotein nitrogen and creatinine rose. There was a better correlation with the duration of nonprotein nitrogen and creatinine elevation. In a number of cases, the values for nonprotein nitrogen and creatinine were above normal, while the urine specific gravity was still above 1.018. This early rise may actually have been due to prerenal azotemia associated with dehydration and sodium chloride loss.

Plasma Chlorides and Carbon Dioxide-Combining Power.—The plasma chlorides remained at normal levels in 61% of the patients. In 39% of the patients, chlorides were lowered sometime between the 2d and 13th days of illness. The lowest levels

TABLE 6.—*Blood Nonprotein Nitrogen and Creatinine in Thirty-One Patients with Hemorrhagic Fever*

	Nonprotein Nitrogen		Creatinine	
	Range	Average	Range	Average
First day of elevation	4-10	7	5-10	7
Day of maximum elevation	5-14	9	4-14	9
Last day of elevation	10-27	17	5-20	10
Maximum level (mg. per 100 cc.)	44-242	106	1.9-16	4.5

ranged between 315 and 420 mg. per 100 ml. (as sodium chloride), and the interval of chloride depression was associated with the interval of severe vomiting.

The carbon dioxide-combining power was low in 68% of the patients. The lowest levels ranged between 23 and 44 vol. % (average of 34) and occurred between the 5th and 12th days of disease (8th day average).

Phenolsulfonphthalein Excretion.—The phenolsulfonphthalein test was performed on 22 patients between the third and sixth weeks of the disease. The results were normal in all cases. It was concluded that either the tests were not done early enough in the course of the disease to demonstrate abnormality or no abnormality of phenol-red excretion existed.

Erythrocyte Sedimentation Rate.—During the acute febrile period, the sedimentation rate remained at normal levels in 30 patients. In 29 of these, it rose to an average of 34 mm. an hour during the second week of illness. By the end of the fifth week of illness, the sedimentation rate had returned to normal in 28 cases. In the fourth week of illness of one patient and the sixth week of three, a secondary elevation to 20 to 27 mm. an hour occurred. The height and period of elevation of the sedimentation rate did not correlate with the severity of illness.

Bleeding Time.—Bleeding time was studied in 26 patients, and in all, it gradually increased, reaching a peak of 3.5 to 51 minutes (18 minutes average) on about the 8th day (range of 7th to 12th day) of illness. The bleeding time returned to normal on the average by the 12th day of illness. In 53% of the patients, a second elevation of the bleeding time to from 3.5 to 24 minutes appeared for several days in the third

week of illness. The relationship between bleeding time, platelet count, capillary fragility, and hemorrhagic manifestations is shown in Chart 4. All patients with an abnormal bleeding time had a platelet depression. The bleeding time and the hemorrhagic manifestations were related in both duration and degree in 70% of the patients. There was direct correlation between the prolongation of bleeding time and increase in capillary fragility in 81% of the patients. In 94% of the patients, the platelet count was diminishing at the time of admission and reached the lowest level, of 30,000 to 190,000, on the seventh day of illness. After the period of depression, the platelet count rose to a peak of 218,000 to 448,000 (330,000 average) on

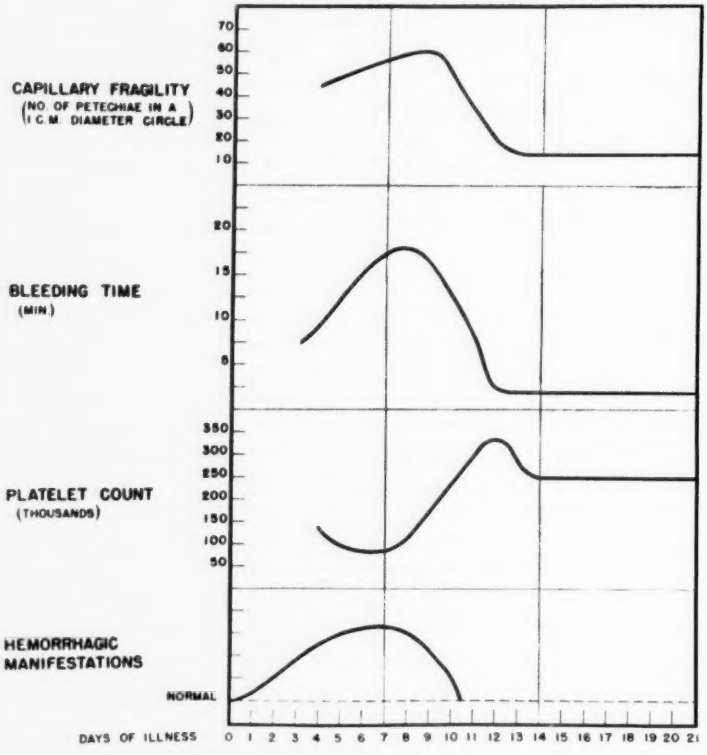


Chart 4.—Duration and intensity of bleeding time, capillary fragility, platelet count and hemorrhagic manifestations in 31 cases of hemorrhagic fever.

the 12th day of illness in 23 patients and subsequently became stabilized at a level slightly below this peak. The degree of platelet depression did not correlate with the severity of disease or extent of bleeding except in the severely ill patients. The duration of the platelet depression was directly related to the duration of bleeding in 21 patients.

Capillary Fragility.—The capillary fragility test was positive in 93% of 29 patients at the time of admission. On about the ninth day of illness, the test was most abnormal, with an average of 60 petechiae per test area, a circle of 1 cm. diameter. The capillary fragility test returned to normal on the 12th day. In nine patients, the test remained positive throughout the course of illness, including the

convalescent phase. Increased capillary fragility was directly correlated to platelet-count depression in 81% of the patients. There were three patients with decreased platelet counts without increases in capillary fragility, and there were three patients with increased capillary fragility and normal platelet counts. Both prolonged bleeding time and increased capillary fragility were present in 81% of the patients. Hemorrhagic manifestations appeared in three patients who had normal capillary fragility tests. In the presence of increased capillary fragility and platelet depression, three additional patients showed no hemorrhagic manifestations.

Miscellaneous Hematologic Studies.—The coagulation time, prothrombin time, and red cell fragility were normal on serial determinations during the acute period of the disease. Clot retraction time varied considerably in each patient, and no conclusions were reached concerning this test. The total eosinophile count was studied in five patients. Counts of 50 or lower were observed during the first week of illness, after which the levels rose, reaching as high as 2,000 by the end of the second week of illness.

Cephalin-Cholesterol Flocculation and Thymol Turbidity.—Cephalin-cholesterol flocculation and thymol turbidity tests were performed at weekly intervals in 17 cases during the period of convalescence. The thymol turbidity ranged between 5 and 10 units on admission. During the course of observation, which varied from 6 to 10 weeks, 29% of the thymol turbidity tests remained unchanged. In 24% of the cases, a further transitory rise occurred before the levels declined to the admission values, and in 47%, a steady decline toward normal occurred. In only 24% did the levels actually reach the normal of 4 units or less.

The cephalin-cholesterol flocculation tests were abnormal in 70% of the patients between the second and fifth weeks of the disease. The period of abnormality was relatively short, and all values returned to normal by the eighth week of illness. Whether the abnormal flocculation tests indicated liver cell damage or merely alterations of the blood proteins associated with an infectious process was not apparent. In one-third of the patients the liver was slightly enlarged and tender on admission, although jaundice was not present.

Miscellaneous Liver Function Tests.—As a further test of liver function, the 5 mg.-per-kilogram sulfobromophthalein sodium (bromsulfalein sodium®) test was performed on 10 patients for whom cephalin-cholesterol flocculation or thymol turbidity tests gave abnormal results. No significant dye retention was present in the 45-minute samples of any of these patients. The serum total protein, albumin, globulin, and albumin-globulin ratio were determined in 26 cases at weekly intervals during the acute and convalescent periods of the disease. No significant changes were observed.

Heterophile Agglutinations.—Heterophile agglutination tests were performed in eight cases during the convalescent period. These tests gave uniformly normal results.

Electrocardiographic Findings.—Table 7 summarizes the abnormal electrocardiographic findings in 31 patients. Sinus bradycardia was observed in electrocardiograms of nine patients during the first three weeks of illness, with rates ranging from 40 to 58. Sinus tachycardia with rates of 115 to 120 occurred in three patients. In two of these, the tachycardia developed during the second week of illness, and in the third, it occurred during the fifth week. The tachycardia followed a period of hypotension in one patient, and in another, it was associated with hemorrhage into the central nervous system. Second degree heart block was seen in one patient

during the first week of disease. This patient was only mildly ill. Four patients showed typical T wave changes associated with hyperpotassemia and acidosis. The tall peaked T waves appeared during the evolution of the uremic state. The Q-T interval calculated according to Bazett's formula was prolonged in five patients during the second and third weeks of the disease. It ranged between 0.44 and 0.48 second. In three patients, this prolongation of electrical systole appeared during the period of maximal renal failure, and in the other two, it appeared during the period of polyuria. Electrolyte disturbance could have accounted for the changes in all cases. Five patients had low or inverted T waves in Leads I and AV_L and the outer chest leads. These T wave abnormalities occurred during the first four weeks of illness and lasted less than one week in all patients.

Spinal Fluid.—A lumbar puncture was performed on each patient at the time of admission. The procedure was repeated on five patients on the second or third day

TABLE 7.—*Electrocardiographic Abnormalities in Thirty-One Patients with Hemorrhagic Fever*

Abnormal Finding	No. of Patients	%	Week of Disease Observed
Sinus bradycardia	9	29	1, 2, 3
Low or inverted T waves in standard and chest leads	5	16	1, 2, 3, 4
Prolonged Q-T interval	5	16	2, 3
Tall, peaked T waves	4	13	2
Sinus tachycardia	3	10	2, 5
Heart block (2d degree)	1	3	1

TABLE 8.—*Spinal Fluid Abnormalities in Thirty-One Patients with Hemorrhagic Fever*

Abnormal Finding	No. of Patients	%	Abnormal Finding	No. of Patients	%
Red blood cells (per cu. mm.)			Total protein (mg. per 100 cc.)		
50-80	2	6	41-50	7	23
Over 1,000	4	13	51-75	5	16
White blood cells (per cu. mm.)			76-100	2	6
5-10	2	6	101-1,000	4	13
Over 10	1	3	Pandy test (1+ or more)	5	16

of hospitalization. Table 8 summarizes the abnormal spinal fluid findings. Spinal fluid pressures were generally within normal limits. Elevated pressures in a few cases were attributed to poor relaxation of the patient. In four patients, the spinal fluid contained gross blood, and in one of these it was xanthochromic. In another patient, the fluid was clear on admission, but 24 hours later, after neurological signs had developed, a second tap revealed bloody fluid. Neurological manifestations accompanied the subarachnoid bleeding in all four cases. Two other patients had 50 to 80 red blood cells per cubic millimeter of spinal fluid, but traumatic taps may have accounted for this finding. Exclusive of the four patients with gross blood in the spinal fluid, 74% of the patients had fewer than 5 white blood cells per cubic millimeter of spinal fluid. Two patients had 6 to 8 lymphocytes and one patient had 26 lymphocytes per cubic millimeter. The total protein level of the spinal fluid was below 41 mg. per 100 ml. in 42% of the patients. In 23%, the protein level was between 41 and 50 mg. per 100 ml., and in 19%, it was over 76 mg. per 100 ml. The Pandy test was positive in only 16% of the patients, each of whom had marked elevation of the spinal fluid total protein. The spinal fluid sugar was normal in all patients.

Venous Pressure and Circulation Time.—The venous pressure and circulation time were recorded in 14 cases between the fifth and eighth days of the disease. Two or more consecutive tests were carried out in five cases. Magnesium sulfate, ether, and papaverine were used in determining the circulation time. All results were within normal limits.

In determining the venous pressure, the patient was placed in a recumbent position on a board supporting the back and outstretched arm. The level of the right atrium was assumed to be 10 cm. above the surface of the back. In 10 patients, the venous pressure was below 120 mm. of saline, and in 4 patients, the pressure ranged between 120 and 175 mm. of saline. No correlation was noted between the level of the venous pressure and the severity of the disease.

CONVALESCENT PERIOD

An average period of two months elapsed between the onset of the illness and the complete disappearance of abnormal signs. In 24 patients, impaired urine-concentrating function was the last abnormal sign, and an average of 54 days was required for the urine specific gravity to reach 1.025. In five patients, the entire duration of illness averaged 52 days. One patient had permanent neurological damage.

TREATMENT

Treatment in this series was symptomatic. Patients were kept in bed and given meperidine hydrochloride for pain, restlessness, or hiccoughs. Atropine was used for nausea and vomiting. Blood lost by hemorrhage was replaced by transfusions of whole blood, and one patient who was admitted in shock received plasma. Dextrose in water was administered intravenously for inadequate oral intake. The amount of fluids administered parenterally and orally was determined on the basis of the intake and output of each patient and was kept to an absolute minimum during the periods of severe oliguria and cardiovascular instability. If the patient was edematous and showed a weight gain, fluids were rigidly restricted. Otherwise, the fluid intake was calculated on the basis of the previous day's output plus 700 cc. for insensible fluid loss. It was noted that many of the hemorrhages were directly related to the trauma of vomiting, retching, and incautious handling. Measures to insure the comfort of the patient and the avoidance of trauma and extremes of temperature undoubtedly were essential in preventing hemorrhage or shock.

COMMENT

Considerable clinical evidence pointed to the capillary as the site principally involved by this disease. In the first few days of illness, the facial flush and mucous membrane injection indicated a generalized capillary dilatation. Abnormal capillary permeability was indicated by the presence of edema in the periorbital, facial, and conjunctival tissues. In the one patient who died, there was massive retroperitoneal tissue edema. It was thought that similar edema contributed to the backache and severe abdominal pain and tenderness that was prominent in these patients. The elevation of the hematocrit reading and hemoglobin content during the first several days of illness may well have been manifestations of the escape of plasma through the capillary walls as well as of simple dehydration. The vascular instability, hypotension, and shock may also have been related to capillary involvement. Other

obvious manifestations of capillary damage were the widespread petechial hemorrhages and the positive capillary fragility tests. Microscopic hematuria and albuminuria early in the disease indicated renal capillary involvement.

GENERAL DESCRIPTION AND SUMMARY

During the autumn of 1951 and winter of 1951-1952, an outbreak of epidemic hemorrhagic fever occurred along the 38th parallel of Korea, chiefly in and around the cities of Kumhwa, Chorwon, and Yonchon. The 31 patients in this series were United Nations personnel from that area. No etiological clue was obtained from their histories of food and water ingestion, individual activities, disease contacts, or past illnesses.

The observed clinical syndrome of epidemic hemorrhagic fever was a composite of nonspecific febrile, cardiovascular, gastrointestinal, renal, and hemorrhagic manifestations with occasional neurological complications. The onset of the disease was usually abrupt, with shaking chills, fever, headache, backache, dizziness, eye pain, and blurred vision. In the first few days, malaise, fatigue, anorexia, nausea, vomiting, and mylagia were added to these symptoms, producing a picture of severe prostration. Almost from the onset, there appeared a deep erythematous flush of the face and neck, injection of the membranes of the soft palate and palpebral conjunctiva, and edema of the face and eyelids. Examination of the patient revealed abdominal tenderness, costovertebral-angle tenderness, moderate lymphadenopathy, and occasional enlargement of the liver or spleen. During the acute febrile period, the patient showed signs of peripheral vascular collapse with hypotension and weak peripheral pulses. Usually, all the symptoms and signs become most intense between the third and seventh days of illness.

As early as the second day, a hemorrhagic tendency was evidenced by petechiae in the axillae and soft palate. These and other signs of hemorrhage reached their height at the end of the first week of illness. During the period of hemorrhage, an increase in capillary fragility, a depression of the platelets, and a prolongation of the bleeding time were found.

Renal involvement made its appearance between the second and fourth days of illness, with microscopic hematuria and albuminuria. The renal aspect of this disease clinically resembled lower-nephron nephrosis. By the end of the first week, the urine output began to decline, reaching the lowest volumes early in the second week. Along with the oliguria, the urine specific gravity fell to low values, and blood nitrogen retention appeared. The renal damage varied from transient abnormalities of the urine to severe uremia.

Toward the end of the second week of illness, many of the symptoms began to subside. The fever was diminished. Hemorrhages appeared with decreasing frequency. Blood pressures returned to normal or high-normal levels. The vascular responses throughout this period showed wide variation, with considerable lability of the pulse and blood pressure. Often a very slow pulse and low diastolic pressure appeared. After a period of diminished urine output of varying duration and degree, the patient had diuresis, with subsequent disappearance of the uremic state.

By the third or fourth week of illness, most of the symptoms and signs had disappeared or were markedly diminished, and during the next few weeks, weight, strength, and renal function returned to normal. There usually was no residual damage or incapacitation.

Dr. Katz's present address is 3873 Grenville Rd., University Heights, Ohio.

LACK OF INTERFERENCE OF AUREOMYCIN WITH PENICILLIN IN TREATMENT OF PNEUMOCOCCIC PNEUMONIA

JAMES J. AHERN, M.D.
AND
WILLIAM M. M. KIRBY, M.D.
SEATTLE

CERTAIN bacteria are destroyed more slowly in vitro when exposed to the combination of penicillin and aureomycin, chloramphenicol, or oxytetracycline ("terramycin") than when exposed to penicillin alone.[1] Antibiotic antagonism has also been observed in experimental mouse infections.[2] Animals that received both penicillin and one of the broad-spectrum antibiotics had a higher mortality rate than those treated with penicillin alone. Effective antibiotic blood levels were present only for a few hours, however, and in similar studies performed in our laboratory no antagonism occurred when blood levels were maintained for two or three days.[3] These observations indicate that antibiotic antagonism is significant mainly during the early hours of antibiotic action and that it may be of clinical importance only when recovery depends upon the rapid destruction of bacteria.

Lepper and Dowling [4] reported a higher mortality rate for patients with pneumococcic meningitis who received both penicillin and aureomycin than for a control group treated with penicillin alone. In pneumococcic meningitis, survival seems to depend upon the rapid destruction of pneumococci, and it is possible that aureomycin interfered with the early bactericidal action of penicillin sufficiently to influ-

From the Department of Medicine, University of Washington School of Medicine, and King County Hospital.

1. Jawetz, E.; Gunnison, J. B., and Coleman, V. R.: The Combined Action of Penicillin with Streptomycin or Chloromycetin on Enterococci in Vitro, Science **111**:254, 1950. Gunnison, J. B.; Jawetz, E., and Coleman, V. R.: The Effect of Combinations of Antibiotics on Enterococci in Vitro, J. Lab. & Clin. Med. **36**:900, 1950. Gunnison, J. B.; Coleman, V. R., and Jawetz, E.: Interference of Aureomycin and of Terramycin with Action of Penicillin in Vitro, Proc. Soc. Exper. Biol. & Med. **75**:549, 1950. Hunter, T. H.: Speculations on the Mechanism of Cure of Bacterial Endocarditis, J. A. M. A. **144**:524, 1950.

2. Jawetz, E., and Speck, R. S.: Joint Action of Penicillin with Chloramphenicol on an Experimental Streptococcal Infection of Mice, Proc. Soc. Exper. Biol. & Med. **74**:93, 1950. Speck, R. S.; Jawetz, E., and Gunnison, J. B.: Studies on Antibiotic Synergism and Antagonism, A. M. A. Arch. Int. Med. **88**:168, 1951. Jawetz, E.; Gunnison, J. B.; Speck, R. S., and Coleman, V. R.: Studies on Antibiotic Synergism and Antagonism, ibid. **87**:349, 1951.

3. Ahern, J. J.; Burnell, J. M., and Kirby, W. M. M.: Lack of Interference of Chloramphenicol with Penicillin in a Hemolytic Streptococcal Infection in Mice, Proc. Soc. Exper. Biol. & Med. **79**:568, 1952.

4. Lepper, M. H., and Dowling, H. F.: Treatment of Pneumococcic Meningitis with Penicillin Compared with Penicillin plus Aureomycin, A. M. A. Arch. Int. Med. **88**:489, 1951.

TABLE 1.—*Summary of Fifty Cases*

Patient	Age	Sex	Day of Illness	Complications on Admission	Type and Source of Pneumococci		Comment
					Sputum	Blood	
				Penicillin Group			
1	42	M	5	None	5	..	Prompt uneventful recovery
2	51	M	15	Overwhelming pneumococcic infection with pericarditis and bilateral empyema	..	1	Death following surgical drainage of empyema on 14th hospital day
3	79	F	8	Arteriosclerotic cardiovascular disease, congestive failure	..	1	Slow recovery requiring 28 days hospitalization; pericarditis developed
4	41	M	2	None	16	..	Prompt uneventful recovery
5	61	F	10	Psoriasis, keratitis, and conjunctivitis	14	14	Pneumonia responded well
6	42	M	2	None	6	..	Prompt uneventful recovery
7	52	M	10	Delirium tremens, inactive pulmonary tuberculosis	..	4	Prompt uneventful recovery
8	57	M	11	Bronchiectasis with recurrent pneumonitis	1	..	Prompt uneventful recovery
9	79	M	15	None	5	..	Delayed resolution
10	47	M	5	Alcoholism	8	..	Prompt uneventful recovery
11	53	M	3	None	9	..	Prompt uneventful recovery
12	68	M	1	Marked pulmonary emphysema	20	..	Prompt uneventful recovery
13	45	M	10	Diabetic acidosis, delirium tremens, auricular fibrillation, congestive heart failure	9	9	Death on 4th hospital day
14	62	M	10	Alcoholism, congestive heart failure, marked obesity	Bile-soluble	..	Slow resolution of pneumonitis
15	67	M	7	None	20	..	Prompt uneventful recovery
16	60	M	2	None	1	..	Prompt uneventful recovery
17	59	M	5	Alcoholism, chronic right upper lobe fibrosis of unknown etiology	1	..	Prompt uneventful recovery
18	48	M	3	Active syphilitic aortitis	18	18	Prompt uneventful recovery
19	74	F	7	Chronic lymphatic leukemia	20	20	Delayed recovery with sterile effusion
20	47	M	7	Alcoholism, pneumonectomy for pulmonary tuberculosis	4	..	Secondary staphylococcic pneumonia cleared with aureomycin
21	83	F	4	Hypertensive arteriosclerotic cardiovascular disease in mild congestive heart failure	5	..	Prompt uneventful recovery
22	51	M	3	Right upper lobectomy for unresolved pneumonia with persistent postoperative pneumothorax	..	10	Secondary enterococcic pneumonia and thrombophlebitis developed; cleared with chloramphenicol and erythromycin
23	38	F	2	Alcoholism, recurrent pneumonia, chronic otitis media, moderate normochromic anemia	5	..	Prompt uneventful recovery
24	53	M	4	Morphine addiction, chronic nephritis, uremia, pericarditis	Group F	..	Death on 4th hospital day
25	83	F	?	Arteriosclerotic cardiovascular disease, senility	9	..	Slightly delayed recovery
				Penicillin-Aureomycin Group			
26	63	M	15	Alcoholic cirrhosis, gout	..	8	Delayed resolution of pneumonitis
27	44	M	8	Alcoholism, patient moribund, massive pulmonary consolidation	15	..	Death in respiratory distress 26 hours after admission
28	83	M	5	Arteriosclerotic cardiovascular disease in mild congestive failure, benign prostatic hypertrophy and cystitis	5	..	Pneumonia responded well
29	86	M	?	Generalized arteriosclerosis; marked senility	5	..	Prompt uneventful recovery
30	51	M	4	Bronchiectasis	29	..	Prompt uneventful recovery
31	27	F	3	Recurrent pneumonia	14	..	Prompt uneventful recovery
32	46	M	1	Alcoholism	8	..	Prompt uneventful recovery
33	49	M	5	Alcoholism, auricular fibrillation, pulmonary emphysema, prostatitis	4	..	Prompt uneventful recovery
34	72	M	3	Pulmonary emphysema with diffuse fibrosis	Bile-soluble	..	Prompt uneventful recovery

TABLE 1.—*Summary of Fifty Cases*—Continued

Patient	Age	Sex	Day of Illness	Complications on Admission	Type and Source of Pneumococci		Comment
					Sputum	Blood	
35	65	M	3	Arteriosclerotic cardiovascular disease in mild congestive failure	..	1	Prompt initial response followed by secondary staphylococcic pneumonia, which cleared with chloramphenicol; multiple cavities followed by fibrosis
36	47	M	12	Auricular fibrillation in congestive failure	..	1	Prompt uneventful recovery
37	82	M	22	Disorientation, senility	5	5	Prompt lysis of fever; small pleural effusion (sterile) and small area of atelectasis developed
38	68	M	8	Inactive pulmonary tuberculosis with fibrosis	3	..	Death on 8th hospital day with overwhelming secondary staphylococcic pneumonia
39	63	M	3	None	3	..	Prompt uneventful recovery
40	48	M	9	Emaciation, disorientation	19	..	Prompt initial response; secondary staphylococcic pneumonia cleared with penicillin and bacitracin
41	73	M	3	None	1	..	Prompt uneventful recovery
42	61	M	?	Gout	22	..	Prompt uneventful recovery
43	45	F	7	Staphylococcic diarrhea	7	..	Prompt uneventful recovery
44	36	F	?	Alcoholism	22	22	Prompt uneventful recovery
45	62	M	?	Cyanosis, disorientation	14	..	Secondary staphylococcic pneumonia cleared with chloramphenicol
46	41	M	3	Alcoholism, recurrent pneumonitis	7	7	Prompt uneventful recovery
47	50	F	3	Diabetic acidosis	9	9	Prompt uneventful recovery
48	48	M	?	Patient moribund; turbid spinal fluid	Group C	Group C	Death on 6th hospital day; autopsy revealed sterile meningitis and endocarditis
49	59	M	4	Alcoholism, delirium tremens	..	9	Secondary staphylococcic pneumonia cleared with chloramphenicol
50	36	F	3	Alcoholism	Group F	..	Prompt uneventful recovery

TABLE 2.—*Comparison of the Two Groups*

	Penicillin Group	Penicillin-Aureomycin Group
Total	25	25
Men	20	20
Women	5	5
Clinical condition		
Severely ill	19	17
Moderately ill	6	8
Average day of illness at admission	6.3	6.4
Average age (yr.)	56.6 (38 to 83)	57.0 (27 to 86)
Average hospitalization (d.)	10.9	11.5
Average duration of antibiotic therapy (d.)	8.4	6.5

ence the course of the disease. With infections in other parts of the body, however, phagocytosis is more effective than in the subarachnoid space,[5] and actual killing of bacteria by the antibiotic is not so essential.

The present study was undertaken to determine whether in pneumococcic pneumonia therapy with penicillin and aureomycin would be more or less favorable than treatment with penicillin alone.

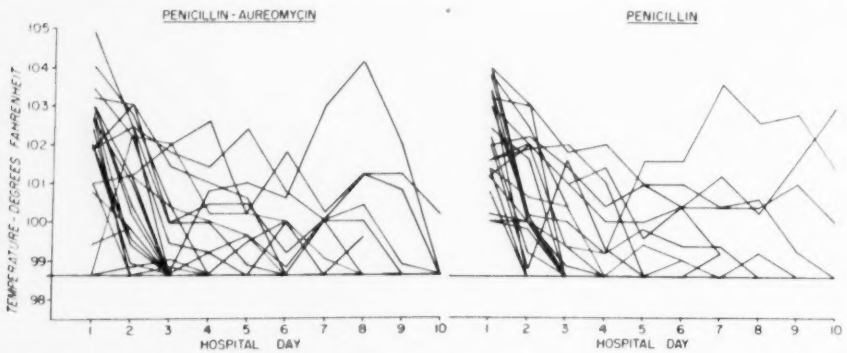
5. Smith, M. R.; Perry, W. D.; Berry, J. W., and Wood, W. B., Jr.: Surface Phagocytosis in Vivo, J. Immunol. **67**:71, 1951.

PLAN OF STUDY

Selection of Patients.—From Dec. 21, 1951, to June 15, 1952, 83 adult patients were admitted to the Infectious Disease Service of the King County Hospital with a diagnosis of bacterial pneumonia. For 33, a specific etiologic agent was not isolated, and these patients were not included in the study. The remaining 50 patients, from whom pneumococci were obtained by blood culture or for whom they were the predominant organism in sputum cultures, were included. None had received antibiotics for their present illness prior to admission to the hospital.

Identification of Pneumococci.—Sputum and blood cultures were made on admission, and pneumococci were typed from the blood agar plate or blood culture bottle. For 46 patients, the specific type of Pneumococcus present in the blood or sputum was identified, typing serum obtained from Wyeth, Inc., being used (Table 1). The infecting organism of two patients reacted with grouping serum but could not be typed. From the other two patients, organisms were recovered which were morphologically typical of pneumococci and were bile-soluble but did not react with typing sera; these were assumed to be pneumococci of "higher types."

Therapeutic Regimen.—Although the patients were not strictly alternated between the two regimens, the two groups were similar in most respects, as indicated in Tables 1 and 2.



Composite temperature charts, showing the similarity in response in the two groups. Complications, chiefly secondary staphylococcic pneumonias, accounted for the instances in which the temperature remained elevated after the third day.

To all patients penicillin G procaine was administered intramuscularly, 600,000 units on admission and 300,000 units every 12 hours thereafter. Aureomycin[6] was given orally, 250 mg. every six hours; to facilitate absorption, the capsules were administered one to two hours before meals with a full glass of water. Two patients were unable to swallow the capsules when first admitted and received 200 mg. of aureomycin intravenously every 12 hours until able to tolerate oral administration. Therapy was continued as long as the clinical course warranted, which was in most instances five to seven days.

RESULTS

In general, the response to therapy was the same in the two groups. In the acompanying chart the maximum daily temperatures of 45 of the 50 patients are charted; the records of the 5 patients in whom fatal complications were present at the time of admission are omitted. Half of the patients in each group were afebrile by the third hospital day (average, 36 hours). Three of the penicillin-treated and one of the combination-treated patients were still febrile on the 10th hospital day; in all four instances the persistent fever was due to a coexisting disease and

6. Aureomycin was supplied by the Lederle Laboratories.

not to the pneumococcic infection. Patients without complications invariably had a prompt clinical response irrespective of the type of therapy they received.

Most of the patients were elderly, poorly nourished, and suffering from one or more chronic disorders. With few exceptions, the patients under 50 years of age were alcoholics, and a number of them had delirium tremens on admission to the hospital. These factors of age, general debility, and alcoholism undoubtedly accounted in large part for the high incidence of bacteremia (34%), complications (24%), and deaths (12%), all of which were equally distributed between the two groups.

Complications that developed during therapy are listed in Table 3. The same number occurred in each group, although they were differently distributed. The penicillin group had a wider variety of complications, whereas in the combination group secondary pneumonia developed more frequently. In none of the patients did gastrointestinal disturbances or moniliasis develop. One superinfection was caused by a penicillin-resistant beta hemolytic Streptococcus which proved to be an Enterococcus (Lancefield Group D), and the patient responded to therapy with erythromycin and chloramphenicol. In six other patients, following an initial

TABLE 3.—*Complications*

	Penicillin Group	Penicillin-Aureomycin Group
Secondary pneumonia		
Staphylococcic	1	5
Enterococcic	1	0
Delayed resolution	2	1
Sterile effusion	1	1
Thrombophlebitis	1	0
Pericarditis	1	0
Total	7	7

response to therapy, there was a return of fever and productive cough, and cultures of the sputum revealed a pure growth of hemolytic Staphylococcus aureus which was penicillin resistant. Pulmonary cavitation occurred in two cases. In five of the six cases of secondary pneumonia, therapy was altered on the basis of in vitro sensitivity tests and consisted of administration of chloramphenicol in two cases, aureomycin in one, penicillin and bacitracin in one, and chloramphenicol, penicillin, and streptomycin in the fifth. All five patients recovered, although multiple cavities followed by fibrosis developed in three. The sixth patient, who was receiving penicillin and aureomycin, died before antibiotic therapy could be changed.

There were three deaths in each group (mortality rate 12%). In three cases, death was due primarily to the pneumococcic infection. One patient (Case 27) was admitted moribund and died 26 hours later. In Case 2 there was bilateral empyema on admission, and the patient died after thoracotomy 14 days later. In the third patient (Case 48) endocarditis and meningitis were found at autopsy, but cultures of these lesions were sterile. In the three other patients, death was due primarily to uremia (Case 24), congestive heart failure (Case 13), and secondary staphylococcic pneumonia (Case 38).

COMMENT

The response of patients with pneumococcic pneumonia to treatment with penicillin and aureomycin was similar to that of a control group treated with penicillin alone. In the uncomplicated cases, subjective and objective signs of improvement occurred promptly with both regimens. Significant interference of aureomycin with the bactericidal action of penicillin should have been readily apparent, since the patients were in general aged, many were chronic alcoholics, and the incidence of bacteremia was high (34%).

In contrast to the results of the present study, Lepper and Dowling [4] observed a higher mortality rate for patients with pneumococcic meningitis treated with penicillin and aureomycin than for patients treated with penicillin alone. These findings were interpreted as indicating that the two antibiotics were mutually antagonistic; i. e., not only that aureomycin interfered with penicillin, but also that penicillin interfered with the action of aureomycin. It was concluded that penicillin and aureomycin should never be administered together, even in the treatment of patients with milder infections, when antagonism has been shown in vitro. The results of the present study are not in keeping with this conclusion, and an alternative interpretation of the results of Lepper and Dowling seems more plausible to us. In the first place, aureomycin and penicillin have not been shown to be mutually antagonistic. The bactericidal action of penicillin is slowed by aureomycin, but the effectiveness of aureomycin is not impaired by the addition of penicillin. In pneumococcic meningitis the killing action of penicillin is probably necessary in most instances to bring about a cure, since phagocytosis has been shown to be relatively ineffective in the subarachnoid space.[5] A few patients have been cured by aureomycin alone, but they probably had milder infections. Slowing of the killing action of penicillin by aureomycin may well have been the determining factor in the patients treated by Lepper and Dowling, resulting in a higher mortality rate for the group treated with both antibiotics.

In pneumococcic pneumonia, on the other hand, the situation is quite different. In the lungs phagocytosis is highly effective, beginning early in the course of the illness. The phenomenon of surface phagocytosis [5] undoubtedly accounts in large part for the fact that bacteriostatic agents such as aureomycin have been as effective as penicillin in the treatment of patients with pneumococcic pneumonia.[7] Since, as noted, the bactericidal action of the two antibiotics in vitro has always been at least as good as that of aureomycin alone, the lack of evidence of antibiotic antagonism in the present clinical study is not surprising.

Pneumococcic meningitis is probably one of the few diseases in which interference of the broad-spectrum antibiotics with penicillin is of clinical significance. With most infections elsewhere in the body, slowing of the bactericidal action of penicillin is of less importance in view of the major role played by the phagocytes. It should be stressed that the present study was undertaken merely for the purpose of evaluating the effectiveness of combined therapy in pneumococcic pneumonia. The fact that interference is not of clinical significance in this disease does not imply

7. Gocke, T. M.; Collins, H. S., and Finland, M.: Aureomycin Treatment of Pneumococcic Pneumonia, Arch. Int. Med. **84**:857, 1949. Dowling, H. F.; Lepper, M. H.; Hussey, H. H.; Caldwell, E. R., and Spies, H. W.: The Treatment of Pneumococcic Pneumonia with Aureomycin, J. Lab. & Clin. Med. **35**:215, 1950.

that more than one antibiotic should be used in therapy. Whenever a single antibiotic is highly effective in the treatment of a given disease, it would appear to be undesirable to add a second agent.

It should be emphasized that our results in no way negate the highly significant in vitro observations of Jawetz [1] concerning the interference of broad-spectrum antibiotics with penicillin. Jawetz has consistently refrained from drawing conclusions concerning the clinical significance of the phenomenon, and it is only through studies such as the present one and that of Lepper and Dowling that implications concerning clinical therapy can be clarified.

A striking feature of the present study was the occurrence of secondary pneumonia caused by staphylococci in six of the patients. Interestingly, five of six infections occurred in patients who received both penicillin and aureomycin. In these instances, the staphylococci were resistant to both aureomycin and penicillin. The one staphylococcic pneumonia in the penicillin-treated group was caused by an organism sensitive to aureomycin, and the patient responded to therapy with that antibiotic. This high incidence of secondary staphylococcic pneumonias is similar to the recent experience of Jackson and associates [8] in treating pneumonia with oxytetracycline. In 48 of 91 patients, Staph. aureus became the predominating organism in the sputum during the course of oxytetracycline therapy, and in 4 patients who died, pathogenic staphylococci were thought to play an important role. It is apparent that antibiotic-resistant staphylococci have become prevalent in certain hospitals and that infections with these organisms are a serious problem.

SUMMARY

The response of 25 patients with pneumococcic pneumonia to penicillin and aureomycin was compared with that of a similar group treated with penicillin alone. The patients were in general aged and debilitated, and many had severe alcoholism. Positive blood cultures were obtained for 17 patients (34%), and there were six deaths (12%), three in each group. From the standpoint of symptomatic improvement, temperature response, disappearance of pulmonary infiltrations, and length of hospitalization, the results were essentially the same in the two groups; i. e., there was no evidence of antibiotic antagonism.

The relationship of these observations to other laboratory and clinical studies of antibiotic interference is discussed, and it is concluded that the phenomenon is probably of clinical importance only in certain diseases, such as pneumococcic meningitis.

Following initial improvement, there was a recurrence of fever, cough, and sputum in 6 of the 50 patients, and Staph. aureus was recovered from the sputum in pure culture. In two of these patients pulmonary cavitation developed, and one patient died.

8. Jackson, G. G.; Haight, T. H.; Kass, E. H.; Womack, C. R.; Gocke, T. M., and Finland, M.: Terramycin Therapy of Pneumonia: Clinical and Bacteriologic Studies in 91 Cases, Ann. Int. Med. **35**:1175, 1951.

OXYTETRACYCLINE-STREPTOMYCIN THERAPY IN BRUCELLOSIS DUE TO BRUCELLA MELITENSIS

GORDON B. MAGILL, M.D.
AND
JOHN H. KILLOUGH, PH.D., M.D.,
CAIRO, EGYPT

ALTHOUGH there have been significant advances in the therapy of acute brucellosis in the past few years, the incidence of post-treatment relapses has remained a problem. In a previous study reported by us there was a relapse rate of 69% following the administration of any one of three antibiotics for an average period of 12 days.[1] Subsequently, efforts to reduce the incidence of relapse proceeded along two lines. One was to prolong administration of a single antibiotic.[2] The other was to use a combination of oxytetracycline ("terramycin") and streptomycin, an approach suggested by the apparent synergism between streptomycin and either aureomycin[3] or oxytetracycline.[4] The present paper reports a study of the latter method in which combined oxytetracycline-streptomycin therapy was administered to 23 patients with acute or subacute brucellosis. The results demonstrate that this form of therapy effects a marked reduction in relapse rate.

MATERIALS AND METHODS

Patients.—Of the 23 patients in this series, 19 had received no previous specific therapy for brucellosis. Four had received one or two courses of a single antibiotic but had relapsed. All the patients were males except one. Ages ranged from 10 to 63 years, averaging 34. As in the

From the United States Naval Medical Research Unit No. 3.

These studies were made possible by the cooperation of the Egyptian Ministry of Health.

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions or assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

1. Killough, J. H.; Magill, G. B., and Smith, R. C.: Terramycin, Chloramphenicol, and Aureomycin in Acute Brucellosis: Preliminary Report, J. A. M. A. **145**:553 (Feb. 24) 1951.

2. Killough, J. H., and Magill, G. B.: To be published.

3. (*a*) Heilman, F. R.: The Effect of Combined Treatment with Aureomycin and Dihydrostreptomycin on Brucella Infections in Mice, Proc. Staff Meet., Mayo Clin. **24**:133 (March 16) 1949. (*b*) Herrell, W. E., and Barber, T. E.: The Combined Use of Aureomycin and Dihydrostreptomycin in the Treatment of Brucellosis, ibid. **24**:138 (March 16) 1949. (*c*) Herrell, W. E., and Barber, T. E.: A New Method for Treatment of Brucellosis, J. A. M. A. **144**:519 (Oct. 14) 1950.

4. Herrell, W. E.; Heilman, F. R.; Wellman, W. E., and Bartholomew, L. G.: Terramycin: Some Pharmacologic and Clinical Observations, Proc. Staff Meet., Mayo Clin. **25**:183 (April 12) 1950.

previous series,[1] patients were selected from among hospitalized patients with undiagnosed fever and with Brucella agglutination titers of 1 : 160 or above. For the 19 previously untreated patients the duration of illness ranged from 2 to 24 weeks, with an average of 8. The total duration of illness for the four patients who had relapsed ranged from 8 to 60 weeks, averaging 30. In 22 patients maximal observed rectal temperatures before therapy ranged from 100.4 to 106.2 F., with an average of 103.0 F. One patient who had a bacteriologic relapse from previous therapy was afebrile when treatment was initiated.

Diagnostic Criteria.—Blood and urine specimens were cultured[5] daily for four days before institution of therapy. Brucella melitensis was isolated from the blood in 22 cases and also from the urine in 12. Brucella agglutinations in these 22 bacteriologically positive cases ranged from 1 : 320 to 1 : 5,120. The one case in which Brucella was not recovered was clinically indistinguishable from the other cases. The patient was the father of two patients with bacteriologically proved brucellosis and had an agglutination titer of 1 : 1,280.

Observations.—During therapy three specimens of blood and one of urine were cultured every week. After therapy patients were kept in the ward for 30 days, during which at least 12 more cultures each of blood and urine were made. If there was no evidence of either clinical or bacteriologic relapse during this period, the patients were discharged. Subsequently they were seen regularly as outpatients and checked with interval histories and physical examinations, routine laboratory tests, and cultures of blood and urine. All were observed from 4 to 17 months (average, 9 months) after completion of therapy.

Method of Therapy.—Oxytetracycline[6] was given orally every four hours, and streptomycin or dihydrostreptomycin[7] was administered concomitantly once a day by intramuscular injection. Of the 23 patients, 21 received 3.0 gm. of oxytetracycline daily for the first week and 1.5 gm. daily for the subsequent two weeks. In addition, these patients received 1.0 gm. of streptomycin daily for the three-week period. The total for each of 21 patients, then, was 42 gm. of oxytetracycline and 21 gm. of streptomycin. One patient, aged 10 years, was treated with half-doses of both antibiotics. Therapy of the other patient was varied because of an unusually resistant infection and will be reported in detail hereafter.

RESULTS

Clinical Response to Therapy.—A typical response to combined treatment is illustrated in Chart 1. After institution of therapy patients became afebrile in from 3 to 7 days (average, 4.6). Symptoms such as arthralgia, headache, and malaise persisted longer than fever, requiring an average of about eight days to disappear.

Bacteriologic Response.—Blood cultures were still positive 24 to 48 hours after institution of therapy in seven cases. They remained positive in two of these at the fifth day and in one at the seventh day. There was no correlation between persistence of bacteremia and either rate of clinical response or tendency to relapse.

Complications During Treatment.—Of the 22 patients who received combined therapy for three weeks, four showed an increase both of fever and of symptoms within 48 hours after institution of therapy. Another eight demonstrated one or

5. A modified version of Castaneda's procedure was used for culture of Brucella organisms. The bacteriologic studies were performed by James E. Samsell (HMI), U. S. N., Othmar C. Dierkhising (HMC), U. S. N., and Billy H. Cook (HMC), U. S. N.

6. Oxytetracycline was supplied through the courtesy of Dr. Gladys I. Hobby, of Chas. Pfizer & Company, Inc.

7. Eleven patients received streptomycin; the other 12, dihydrostreptomycin. For clarity in subsequent discussion streptomycin will be considered synonymous with dihydrostreptomycin.

the other of these phenomena. Thus a total of 12 (55%) of the patients experienced a Herxheimer-like reaction when first given treatment, but in none was it severe or prolonged.

As to possible toxic effects of therapy, four patients complained of slight transient dizziness. In none of these was there objective evidence of vestibular or auditory disturbances. Ten patients noted slight anorexia, and two of these had an episode of vomiting after institution of therapy. These and other gastrointestinal disturbances were minimal and disappeared with reduction of oxytetracycline dosage after the first week. That the transient side-effects were probably of little significance is shown by the fact that during therapy 19 patients gained 3 to 16 lb. (1.3

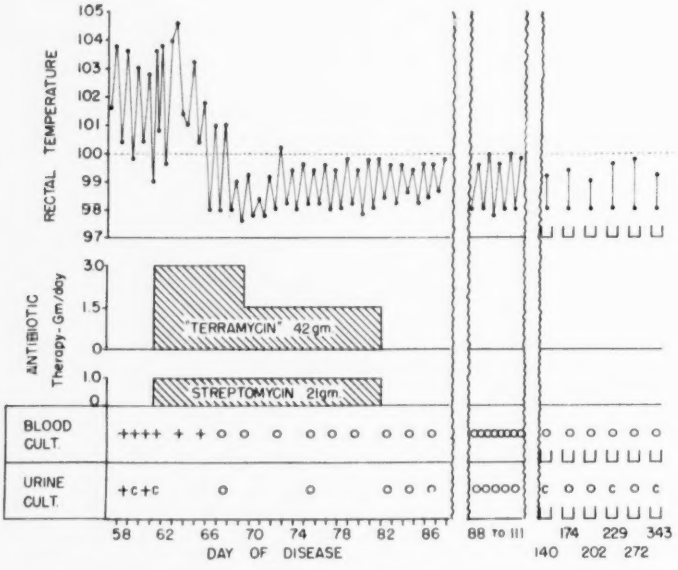


Chart 1.—Response to oxytetracycline and streptomycin therapy in a patient with acute brucellosis. After institution of therapy there was a transient increase in both fever and symptoms. Blood cultures were still positive on the fifth day of treatment; *c* indicates contaminated cultures; + and o represent, respectively, positive and negative cultures.

to 7.3 kg.) and the weight of two remained unchanged. One patient lost 12 lb. (5.4 kg.), possibly owing to severe hepatitis with anorexia which was present on admission and persisted until the 18th day of therapy. This patient subsequently gained weight, even when re-treated for a relapse with increased dosage of oxytetracycline plus streptomycin.

Other complications that developed during therapy consisted of a painful subcutaneous nodule over the right elbow in one patient and epididymitis in another. Both these complications occurred during the first week and subsided spontaneously during continued therapy.

Complications Following Treatment.—A second case of transient epididymitis developed in a 10-year-old boy on the 11th post-treatment day. This episode was

accompanied by several low-grade spikes of fever, the highest being 100.4 F. It was felt that the episode represented a complication of repeated difficulties in catheterization of the patient rather than a manifestation of brucellosis. The patient was observed for more than nine months after treatment and had no further febrile episodes. Likewise, he had consistently negative blood and urine cultures after therapy.

Relapses.—Of the 22 patients treated for three weeks, 3 (14%) relapsed. One patient had a single temperature elevation of 100.6 F. on the eighth post-treatment day. For the following 10 weeks he remained asymptomatic, and then suddenly a full-blown clinical relapse with high fever and positive blood and urine cultures developed. Another clinical relapse occurred 20 days after treatment, but the organism was not isolated from the patient in spite of 24 post-treatment cultures. Both these patients were re-treated with oxytetracycline plus streptomycin with increased doses of the former (4.5 gm. daily for the first week and then 2.25 gm. daily for the subsequent two weeks). They were observed more than six months after re-treatment and showed no evidence of another relapse. The third relapse was bacteriologic, without clinical signs, in a patient who had a positive blood culture four months after therapy. This patient was not re-treated, because subsequent cultures were negative and the patient continued to deny symptoms.

Unusual Resistance to Therapy.—One patient showed an unusually severe, resistant infection, requiring much more treatment than the other 22 patients, and his case is reported here.

REPORT OF A CASE

A 35-year-old Egyptian farmer was admitted with a history of fever, chills, headache, and weakness for 25 days and multiple joint pains for 14 days. Penicillin and sulfadiazine therapy at another institution had been ineffective, and the patient had continued to note increasingly severe symptoms.

Physical examination revealed an acutely ill, febrile man who was perspiring freely. Blood pressure was 120/65. There was moderate generalized lymphadenopathy. At the cardiac apex there was a loud systolic murmur preceded by a faint rumbling presystolic murmur. In addition, there was a high-pitched mid-diastolic murmur along the left sternal border and a high-pitched systolic murmur at the cardiac base, transmitted into the neck. Both the liver and the spleen were palpable 5 cm. below the costal margin and both were tender.

Laboratory examination revealed a Brucella agglutination titer of 1:1,280; red blood cell count, 3,890,000; hemoglobin, 10.8 gm. per 100 ml., and leucocytic count, 4,850, with a normal differential count. Liver-function studies showed sulfobromophthalein retention of 9% at 45 minutes; serum bilirubin of 0.6 mg. per 100 ml., and thymol and zinc turbidities of 8.6 and 18.4 units, respectively. A chest roentgenogram was negative. An electrocardiogram revealed left bundle branch block. Blood and urine cultures were positive for Br. melitensis.

On the fourth hospital day administration of oxytetracycline was started in a dosage of 3.5 gm. a day and continued for 11.5 days (Chart 2). After this course the patient relapsed, was re-treated with 82 gm. of oxytetracycline in 15.5 days, relapsed again and was re-treated, this time with 88 gm. of chloramphenicol in 14 days. After a third relapse it was decided to treat the patient again with chloramphenicol but to prolong the course and reduce the dosage when he became afebrile. However, the patient became febrile with the reduced dosage, and it had to be increased again. This second course of chloramphenicol totaled 100 gm. in 44 days. Nine days later the patient was again febrile and blood cultures were positive. Oxytetracycline therapy was reinstituted and the temperature returned to normal. As with chloramphenicol, however, fever returned when the dosage was reduced. In addition, the blood cultures were positive in

spite of the antibiotic. In view of the fact that this patient had an organism resistant to the usual doses of chloramphenicol, oxytetracycline, and aureomycin, as evidenced by clinical observations and by laboratory sensitivity studies, it was decided to initiate combined therapy. Streptomycin, 1 gm. a day, was added on the 32d day of oxytetracycline therapy. Even with this combined therapy the patient failed to show improvement and continued a slow downhill course. Upper-abdomen pains became severe, and there was marked increase in size and tenderness of both liver and spleen. Since there was still no improvement after 10 days of combined therapy, the dosage of oxytetracycline was increased to 3.0 gm., and then finally to 6.0 gm. a day, and administration of streptomycin was continued as previously. With this therapy the patient became afebrile in six days, and both liver and spleen gradually decreased in size and tenderness. Although anorexia and nausea occurred, there was marked subjective improvement, and even these minor toxic symptoms gradually disappeared over a period of four weeks. Therapy was

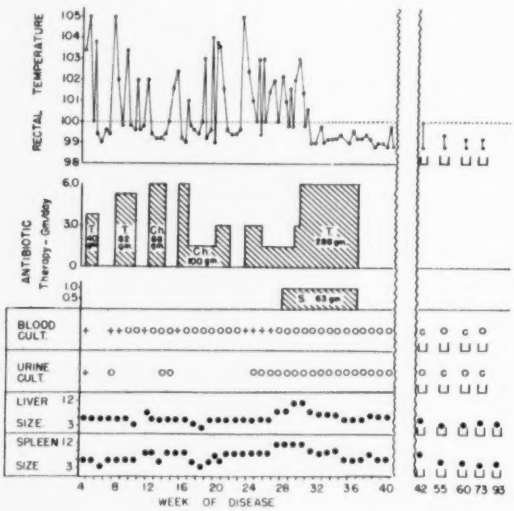


Chart 2.—Summary of an unusually severe, resistant infection with repeated post-treatment relapses in a 35-year-old man (case report). Patient required large doses of oxytetracycline with streptomycin to effect a sustained remission. Points on the temperature curve represent maximum recorded rectal temperatures at half-week intervals. *T* indicates "terramycin"; *Ch.*, chloramphenicol; *S.*, streptomycin. Liver and spleen sizes are in terms of centimeters below the costal margins.

continued until the patient had been afebrile for six weeks. The last course consisted of 288 gm. of oxytetracycline in 84 days and 63 gm. of streptomycin in 63 days.

Observation in the ward was continued another 30 days. During this time the patient remained afebrile and asymptomatic, and 28 cultures of blood and urine were negative for Brucella. In the 16 months following discharge he remained asymptomatic, and an additional 12 blood and urine cultures were negative. Brucella agglutination titer recently was 1:320. The liver and spleen diminished further in size and at the last examination represented what is probably the "normal" for one who works in canals infested with Schistosoma (Bilharzia). At that time there was no change in cardiac findings, including those of the electrocardiogram.

The presence of such a resistant infection in a patient with evidence of aortic valvular disease raised the question of Brucella endocarditis, a well recognized,

though uncommon, entity.[8] The presence of bundle branch block and the absence of changing quality or character of the cardiac murmurs, however, were strong evidence against that diagnosis.

COMMENT

The most outstanding result from the present series of cases is the marked reduction in relapse rate following combined therapy with oxytetracycline and streptomycin. In a preliminary study we reported a relapse rate of 69% following the administration of a single antibiotic (oxytetracycline, chloramphenicol, or aureomycin) for an average period of 12 days.[1] Continued follow-up of the patients for a period comparable to that in the present series revealed four more relapses. Two of these were clinical, one with bacteriologic confirmation; the other two were bacteriologic without clinical signs. The actual relapse rate in the initial series, then, was 31 of 39 cases, or 80%. In contrast, only 3 (14%) of 22 patients in the present study relapsed after combined therapy for 21 days. In both groups one-third of the relapses were of the asymptomatic, bacteriologic variety. Since the two groups were clinically similar and had comparable follow-up studies, the overall reduction in relapse rate cannot be explained by variations in these factors.

In regard to post-treatment relapses, two important questions arise about the combined therapy. First is the question as to whether streptomycin used concomitantly with another antibiotic is superior to a single antibiotic administered for an equal period. The results reported with the combination of aureomycin and streptomycin [3c] were superior to those noted with aureomycin or chloramphenicol alone administered for comparable periods.[9] Further evidence indicating the superiority of combined therapy in this respect is found in a comparison of the present study with our initial series. Four of the patients in the first series received a single antibiotic for 19 to 23 days. Of these four, two had illnesses of average severity; the other two were severely ill, but no more so than some of the patients in the present study. All four patients relapsed after therapy. In contrast, there were only three relapses in the present series of 22 patients given the combined therapy for a similar period (21 days).

The second question concerns the length of administration. Herrell and Barber [3c] reported excellent results from aureomycin and dihydrostreptomycin given for 12 to 14 days to 21 patients with bacteremic brucellosis. More recently they have

8. Spink, W. W., and Nelson, A. A.: Brucella Endocarditis, Ann. Int. Med. **13**:721 (Oct.) 1939. Spink, W. W.; Titrud, L. A., and Kabler, P.: A Case of Brucella Endocarditis with Clinical, Bacteriologic, and Pathologic Findings, Am. J. M. Sc. **203**:797 (June) 1942. Harris, H. J., and Stevenson, B. L.: Brucellosis (Undulant Fever): Clinical and Subclinical, Ed. 2, New York, Paul B. Hoeber, Inc., 1950. Spink, W. W.; Hall, W. H., and Magoffin, R.: Follow-Up Study of Therapy in 48 Culturally Proved Cases of Brucellosis; Streptomycin and Sulfadiazine, Aureomycin, and Chloramphenicol (Chloromycetin), A. M. A. Arch. Int. Med. **88**:419 (Oct.) 1951.

9. (*a*) Spink, W. W.; Braude, A. I.; Castaneda, M. R., and Silva-Goytia, R.: Aureomycin Therapy in Human Brucellosis Due to Brucella Melitensis, J. A. M. A. **138**:1145 (Dec. 18) 1948. (*b*) Braude, A. I.; Hall, W. H., and Spink, W. W.: Aureomycin Therapy in Human Brucellosis Due to Brucella Abortus, ibid. **141**:831 (Nov. 19) 1949. (*c*) Knight, V.; Ruiz-Sanchez, F., and McDermott, W.: Chloramphenicol in the Treatment of the Acute Manifestations of Brucellosis, Am. J. M. Sc. **219**:627 (June) 1950.

ascribed similar results with oxytetracycline plus dihydrostreptomycin.[10] In their series infections with each species of Brucella were present, and therefore the results cannot be compared directly with ours. The occurrence of 14% of relapses in the present series of caprine infections treated for 21 days suggests that the total period of combined therapy should be no less than three weeks when one is dealing with Br. melitensis.

A similar reduction in relapse rate has been noted in a comparable series of patients treated with oxytetracycline alone for a prolonged period (six weeks). The relative advantages and disadvantages of these regimens are discussed in the report of that series.[2]

One patient in the present series and five in the initial study relapsed between two weeks and five months after discharge. The possibility cannot be ruled out that these episodes might have been due to reinfection. In view of the known latency of Brucella infections, however, such recurrences have been considered to be relapses.

The rather frequent occurrence of a Herxheimer-like exacerbation after institution of therapy deserves comment. In no case was it severe or accompanied by a shock-like picture, as noted by Spink and associates.[9a] The incidence of this reaction was twice as great with combined therapy (55%) as it was with one antibiotic alone in our initial study (28%). If, as suggested by others,[11] the reaction is due to the sudden destruction of large numbers of the infecting organism, perhaps the higher incidence of this type of reaction implies a more effective direct action on Brucella than that accomplished by one antibiotic alone.

It is apparent that, although the 14% relapse rate in the present series represents a marked reduction from the initial series, relapses are still a significant problem in the therapy of brucellosis due to Br. melitensis. Final solution of this problem apparently must await the discovery of agents more effective than the currently available antibiotics.

In the general management of patients with the acute symptoms of brucellosis it would be desirable to alleviate symptoms more rapidly after institution of therapy. With both single and combined antibiotic therapy it required from three to seven days for patients to become afebrile and about twice as long to eliminate the other symptoms of the infection. The well-known effects of cortisone against fever and arthralgia [12] suggested a trial of this agent in the therapy of acute brucellosis. Studies utilizing cortisone plus oxytetracycline and streptomycin are now under way and will be reported subsequently.

10. Herrell, W. E., and Barber, T. E.: Treatment of Brucellosis with Aureomycin or Terramycin Combined with Dihydrostreptomycin, Postgrad. Med. **11**:476 (June) 1952.

11. Moore, J. E., and Others: The Modern Treatment of Syphilis, Ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1941.

12. Hench, P. S.: The Reversibility of Certain Rheumatic and Nonrheumatic Conditions by the Use of Cortisone or of the Pituitary Adrenocorticotropic Hormone, Ann. Int. Med. **36**:1 (Jan.) 1952. Smadel, J. E.; Ley, H. L., Jr., and Diercks, F. H.: Treatment of Typhoid Fever: I. Combined Therapy with Cortisone and Chloramphenicol, ibid. **34**:1 (Jan.) 1951. Woodward, T. E.; Hall, H. E.; Dias-Rivera, R.; Hightower, J. H.; Martinez, E., and Parker, R. T.: Treatment of Typhoid Fever: II. Control of Clinical Manifestations with Cortisone, ibid. **34**:10 (Jan.) 1951.

SUMMARY

Twenty-three patients with acute or subacute brucellosis due to Br. melitensis were treated with a combination of oxytetracycline ("terramycin") and either streptomycin or dihydrostreptomycin.

Twenty-two patients received both antibiotics for three weeks. As in a previous study with a single antibiotic, clinical response in the present series was good and control of acute symptoms was adequate. A transient Herxheimer-like reaction was noted in 55% of cases, but in no instance was it severe. The 14% of relapses in the present series represents a marked reduction from the 80% relapse rate noted in the previous study.

A case is reported in which a highly resistant infection was brought under control only after the administration of large doses of oxytetracycline with streptomycin for a prolonged period.

INVOLVEMENT OF BONE MARROW IN DIFFUSE PULMONARY DISEASE

AUSTIN S. WEISBERGER, M.D.
AND
ROBERT M. DUMM, M.D.
CLEVELAND

THE ROENTGENOGRAPHIC appearance of discrete miliary opacities or diffusely distributed pulmonary lesions often presents a difficult diagnostic problem. The differential diagnosis includes miliary tuberculosis, sarcoidosis, fungus disease, metastatic carcinoma, pneumoconiosis, and pulmonary fibrosis, as well as many less common diseases.[1] Diffuse involvement of the pulmonary parenchyma sufficient to produce a miliary-nodule appearance roentgenographically is frequently associated with disseminated disease. When the diagnosis cannot be established on the basis of bacteriologic, mycologic, or immunologic findings, biopsy of tissue involved by the disease process is desirable. In the absence of enlarged lymph nodes, biopsy of the lung, liver, or marrow may be necessary in order to establish a diagnosis. Lung biopsy is a comparatively radical procedure, whereas needle biopsy of the liver or examination of the marrow is easily performed and may furnish valuable information. In order to investigate this problem, the sternal marrow was studied in 24 patients with diffusely distributed pulmonary lesions and compared with the findings for 25 patients with known far-advanced pulmonary tuberculosis.

METHODS AND MATERIAL

Sternal marrow aspirations were performed on 24 consecutive patients with roentgenographic findings of discrete miliary opacities or diffusely distributed pulmonary lesions (Tables 1 and 2) for most of whom no diagnosis had been established. Similar studies were made on 25 patients with known far-advanced pulmonary tuberculosis.

The marrow particles obtained by aspiration were separated and collected in plasma, which was then clotted with 0.25 M calcium chloride. The resultant clot containing the marrow particles was placed in Zenker's acetic fixative for 30 minutes to 1 hour. Sections of the marrow particles were made by routine histologic technique. Details of the methods employed have been described previously.[2] Samples of marrow were obtained by surgical trephine from two patients in whom repeated aspirations failed to yield sufficient material for examination (Patients 4 and 7, Table 1). Whenever possible the diagnosis was later established or confirmed by other means.

From the Department of Medicine, Lakeside Hospital, and the School of Medicine, Western Reserve University.

1. Felson, B.: Acute Miliary Diseases of the Lung, Radiology **59**:32-48, 1952.

2. Weisberger, A. S., and Heinle, R. W.: Study of Fixed Tissue Sections of Sternal Bone Marrow Obtained by Needle Aspiration: I. Method and the Morphology in Various Conditions, Am. J. M. Sc. **215**:170-176, 1948.

Routine bacteriologic and immunologic studies were performed for all patients. Biopsy of available lymph nodes, skin, tonsils, or liver was done whenever indicated. Lung biopsies were performed for three patients.

RESULTS

Of the 24 patients with roentgenographic evidence of diffusely distributed pulmonary lesions, 9 showed a pathologic lesion in the marrow (Table 1). In the

TABLE 1.—*Cases with Roentgenographic Evidence of Diffuse Pulmonary Nodulation in Which Lesions Were Found in the Bone Marrow*

Case No.	Diagnosis	Comment
1	Miliary tuberculosis	Fever of unknown etiology; diagnosis made by marrow aspiration, later confirmed by gastric lavage
2 *	Miliary tuberculosis	Diagnosis confirmed by lung biopsy; sputum negative; no other diagnostic material available
3	Miliary tuberculosis	Diagnosis established by finding of organisms in sputum
4 †	Sarcoid	Granuloma in marrow obtained by surgical trephine; dry taps on aspiration; diagnosis confirmed by liver biopsy
5	Sarcoid	Diagnosis confirmed by lymph node biopsy
6	Histoplasmosis	Histoplasmin skin test positive
7 †	Histoplasmosis	Granuloma in marrow obtained by surgical trephine; dry tap on aspiration; histoplasmin skin test positive
8	Amyloid	Lesions first found in marrow; diagnosis confirmed by lymph node biopsy
9	None	Case continues to be undiagnosed

* Diagnosis confirmed by lung biopsy.
† Surgical trephine required to obtain marrow.

TABLE 2.—*Cases with Roentgenographic Evidence of Diffuse Pulmonary Nodulation in Which No Lesion Was Found in the Bone Marrow*

Case No.	Diagnosis	Comment
1	Miliary tuberculosis	Established by lymph node biopsy
2	Miliary tuberculosis	Organisms found in sputum
3	Miliary tuberculosis	Organisms found in sputum
4	Sarcoid	Tonsils and skin involved
5	Sarcoid (?)	Sarcoid suspected; diagnosis not established
6	Sarcoid (?)	Sarcoid suspected; diagnosis not established
7	Sarcoid (?)	Sarcoid suspected; diagnosis not established
8	None	Roentgenographic findings only
9	None	Roentgenographic findings only
10	None	Roentgenographic findings only
11	Berylliosis	Far advanced
12	Pulmonary fibrosis *	Confirmed by lung biopsy
13	Pulmonary fibrosis *	Confirmed by lung biopsy
14	Pulmonary fibrosis †	Autopsy diagnosis
15	Pulmonary fibrosis	Clinical diagnosis

* Confirmed by lung biopsy.
† Confirmed by postmortem findings.

remaining 15 patients the marrow was normal histologically. Bone marrow lesions were not found in any of the 25 patients with far-advanced pulmonary tuberculosis.

Of the nine patients with histologic lesions in the marrow, three had miliary tuberculosis (Figs. 1, 2, and 3), two had sarcoidosis (Figs. 4 and 5), two had histoplasmosis (Figs. 6 and 7), one had amyloidosis (Fig. 8), and the condition of one remained undiagnosed (Fig. 9). The condition of two patients with miliary tuberculosis was undiagnosed prior to the finding of a miliary tubercle in the marrow sections (Patients 1 and 2, Table 1). The diagnosis was subsequently confirmed

by bacteriologic methods for one of these two patients and by lung biopsy for the other. The diagnosis of amyloidosis was also first established by the marrow findings and was later substantiated by lymph node biopsy (Patient 8, Table 1). The two patients with histoplasmosis did not have enlarged lymph nodes considered suitable

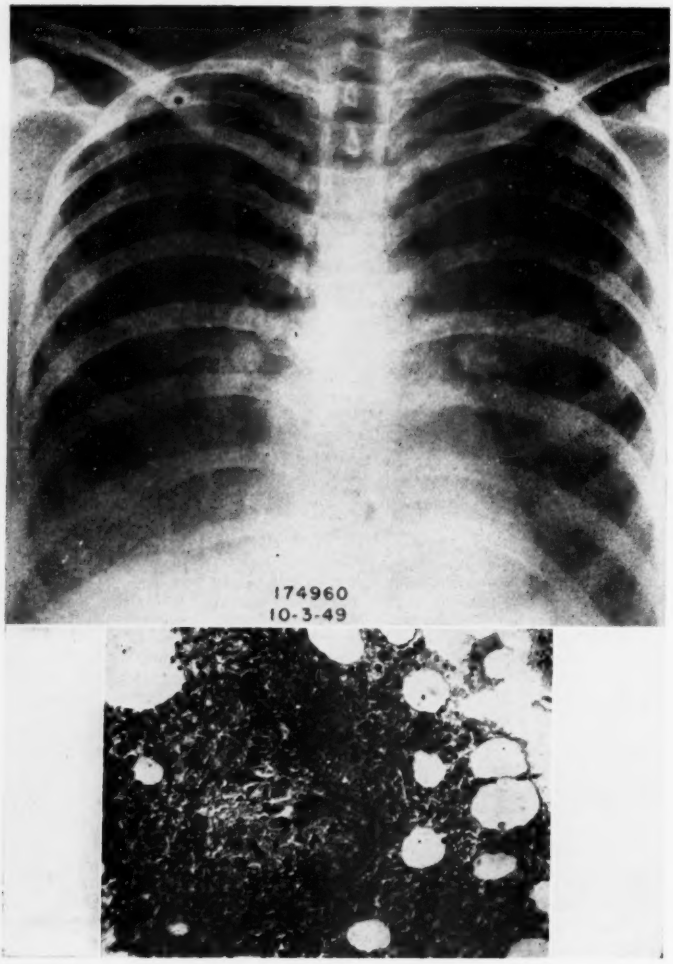


Fig. 1.—Miliary tuberculosis of lung with miliary tubercle in marrow.

for biopsy. A presumptive clinical diagnosis was made for these two patients because of the presence of fever, discrete pulmonary miliary opacities, and a positive histoplasmin skin test. Although no histoplasmosis organisms were seen on the marrow films, the finding of a granuloma in the marrow sections was in keeping with the diagnosis of histoplasmosis. Unfortunately, marrow cultures were not obtained.

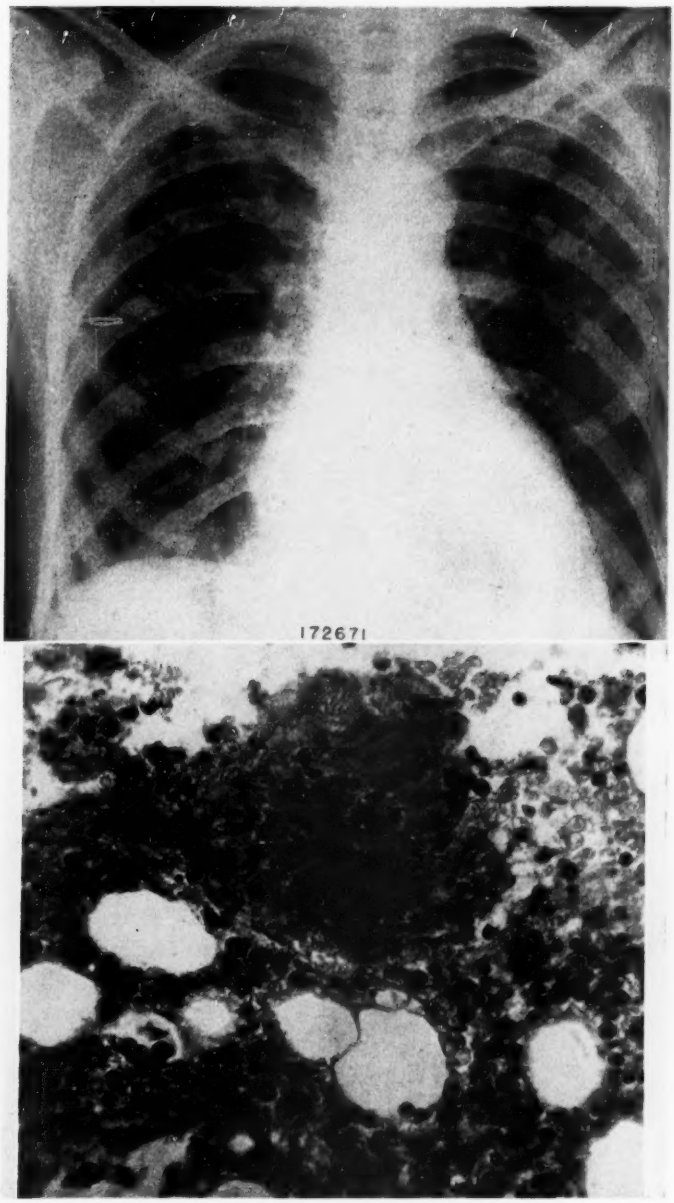


Fig. 2.—Miliary tuberculosis of lung with miliary tubercle in marrow.

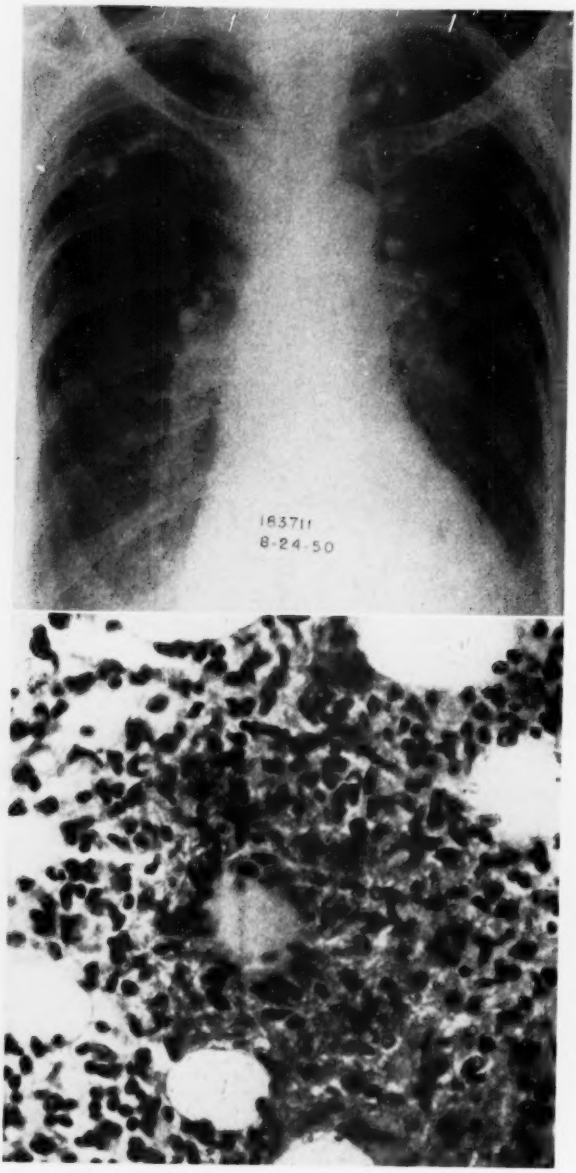


Fig. 3.—Miliary tuberculosis of lung with miliary tubercle in marrow.

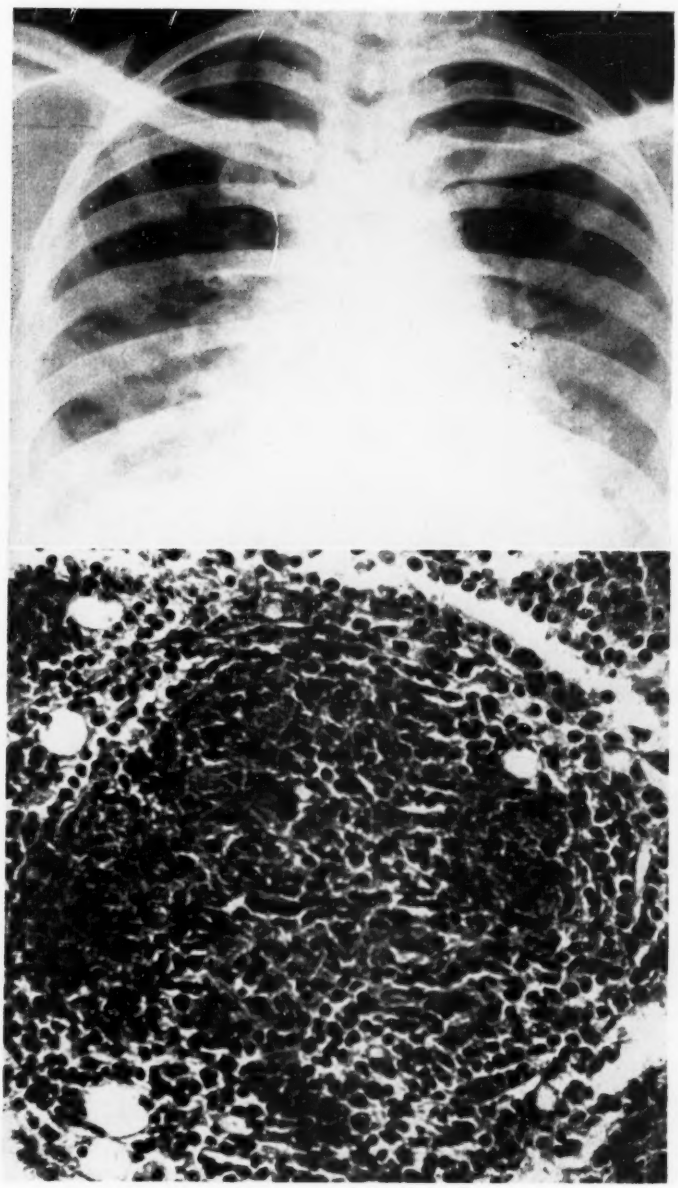


Fig. 4.—Sarcoidosis of lung with involvement of marrow.

The marrow was extensively involved and to a great extent replaced by the lesions in the two patients with sarcoidosis and in the patient with amyloidosis. These patients had anemia, leucopenia, and thrombocytopenia. No constant pattern was present in the peripheral blood of the remaining patients. In these, normal activity of the surrounding marrow was observed despite focal involvement of the marrow by the disease process.

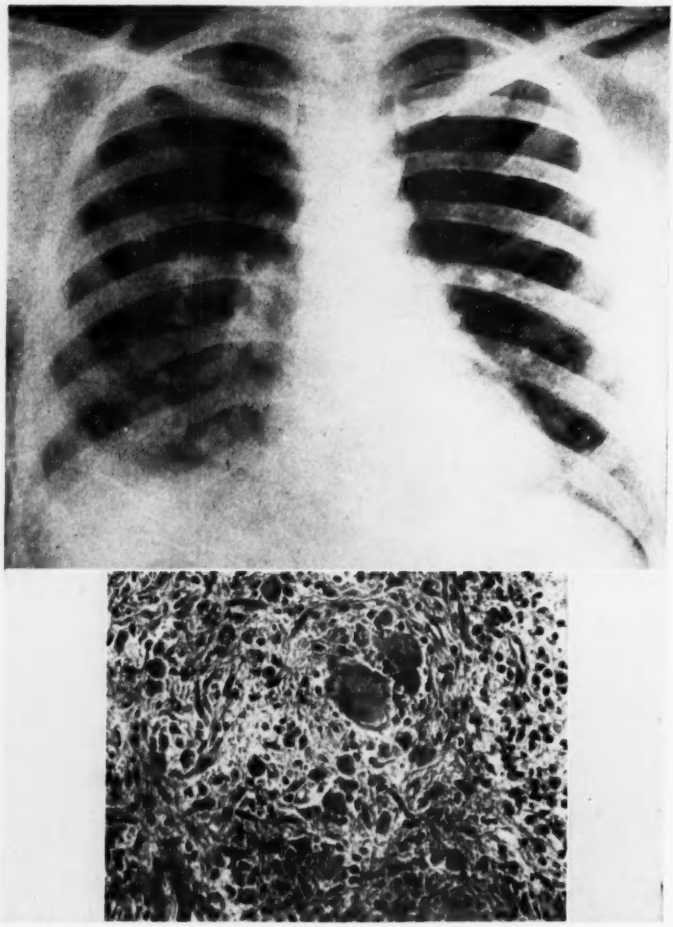


Fig. 5.—Sarcoidosis of lung with involvement of marrow.

Of the 15 patients with roentgenographic findings of diffusely distributed pulmonary lesions in whom no lesion was found in the marrow, three had proved miliary tuberculosis. One had proved sarcoidosis and three suspected, but not proved, sarcoidosis. Four of the patients had diffuse pulmonary fibrosis of unknown etiology, the diagnosis being confirmed for two by lung biopsy and for one by postmortem examination. One patient had extensive berylliosis. Three cases remain undiagnosed.

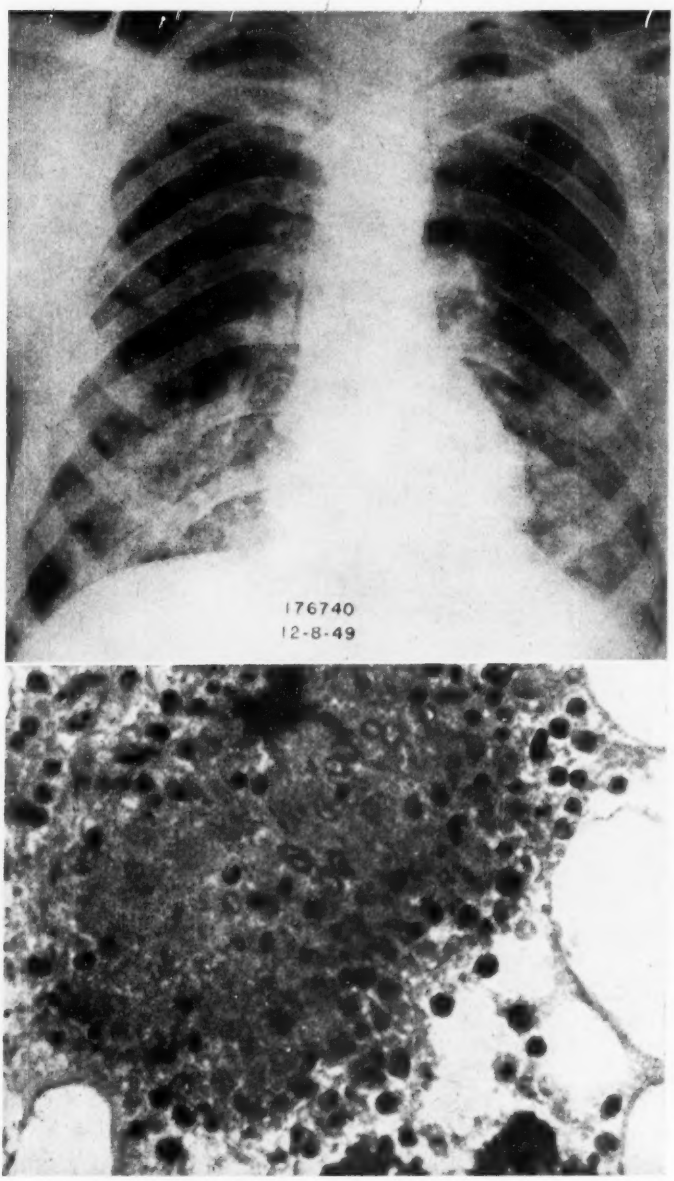


Fig. 6.—Histoplasmosis involving lung and marrow.

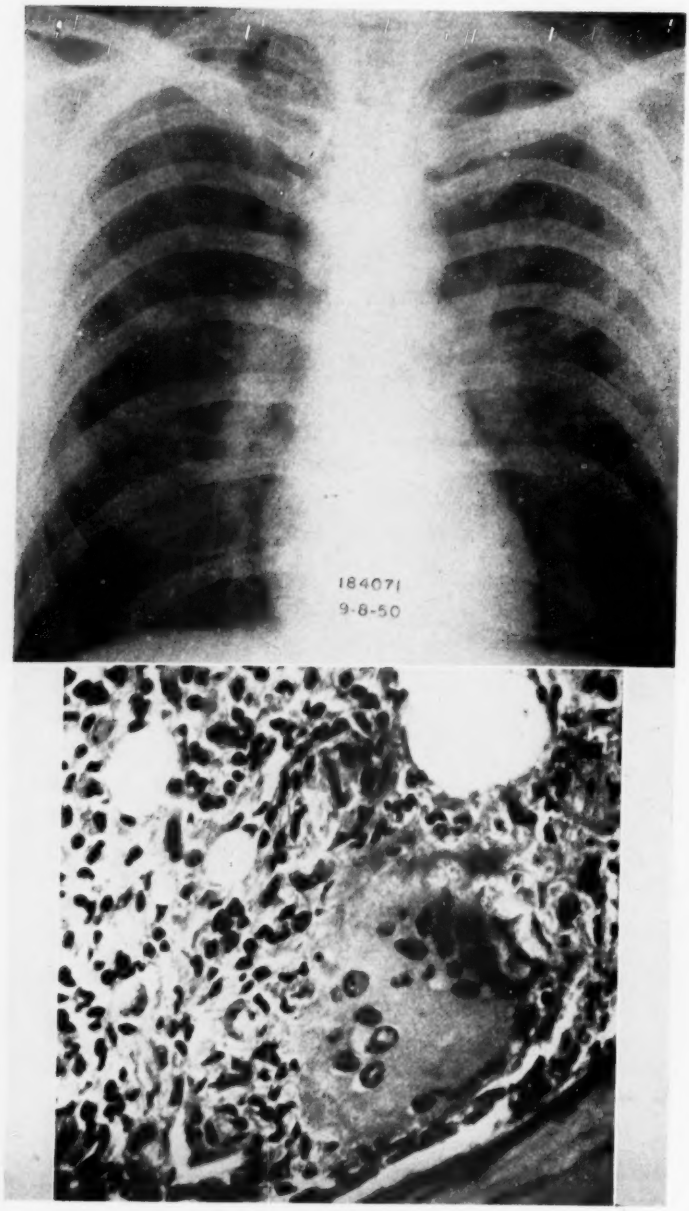


Fig. 7.—Histoplasmosis involving lung and marrow.

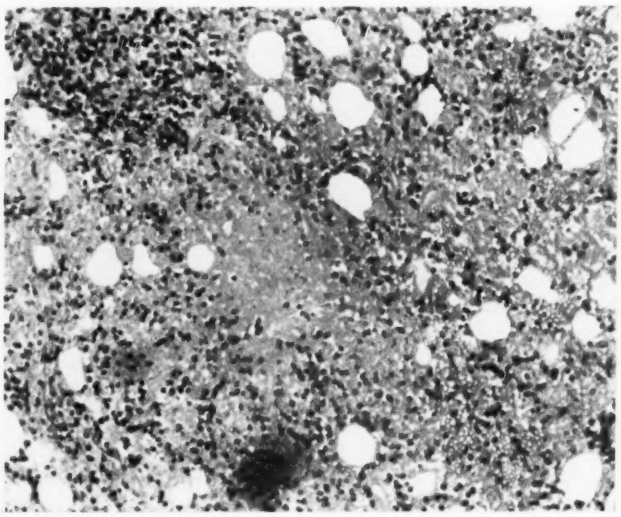


Fig. 8.—Amyloid involvement of marrow in a patient whose chest x-ray showed diffuse nodular infiltration.

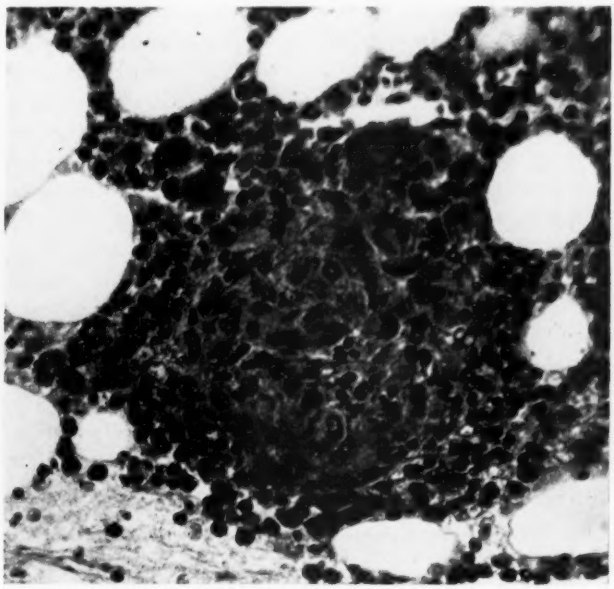


Fig. 9.—Granuloma found in marrow by needle aspiration. Diffuse pulmonary nodulation was apparent roentgenographically. Etiology was undetermined.

COMMENT

Involvement of the bone marrow was demonstrated in 9 of 24 patients with roentgenographic findings of diffusely distributed pulmonary lesions. Of the 15 patients in whom a marrow lesion was not demonstrated, several had disease limited to the lungs. Thus, 4 of the 15 were found to have pulmonary fibrosis (Patients, 12, 13, 14, and 15, Table 2). The diagnosis was not definitely established for 6 of the remaining 11 patients, and some of these probably did not have disseminated disease.

Except in the patient with amyloid, all the lesions found in the marrow were granulomas. Five of the eight granulomas found were either miliary tubercles or sarcoid. The marrow findings were diagnostic for three of six patients with miliary tuberculosis and for two of three patients with proved sarcoid. For several patients, the diagnosis was first established on the basis of the marrow findings (Table 1) and was later confirmed by other diagnostic material. The presence of miliary tubercles in aspirated marrow particles has been demonstrated previously by Stahel [3] and by Schleicher.[4] Nickerson [5] found that sarcoid frequently involved the marrow in autopsy material. Sundberg found granulomas in aspirated marrow particles in four of nine patients with brucellosis. Histologic examination of the marrow is indicated, therefore, whenever a disseminated granulomatous disease is suspected or when the roentgenographic findings of diffusely distributed pulmonary lesions present a diagnostic problem.

In one of the patients a granuloma was found on liver biopsy as well as on bone marrow examination (Patient 4, Table 1). This fact is further evidence that discrete pulmonary nodulations may be associated with disseminated disease. Liver biopsy may be of diagnostic value when the bone marrow examination is negative.

Extensive involvement of the lung is not always associated with disseminated lesions. Thus, none of the patients with far-advanced pulmonary tuberculosis were found to have lesions in the bone marrow, the marrow being involved only in patients with miliary tuberculosis. The occurrence of bone marrow involvement can be correlated with the presence of diffuse miliary nodulations rather than with the amount of lung involvement roentgenographically demonstrable.

The majority of the marrow lesions were demonstrated in histologic sections prepared from marrow particles obtained by needle aspiration. Surgical trephine of the bone may result in a more representative sampling of the marrow and might therefore be of more value in diagnostic problems. Surgical trephine of the marrow is especially indicated whenever repeated aspiration of the marrow results in "dry taps." In two patients (Patients 4 and 7, Table 1) in whom "dry taps" were obtained repeatedly, surgical trephine of the marrow revealed involvement by a granulomatous process.

3. Stahel, R.: Reaktionen um Granulationsgewebe im Knochenmark bei Miliartuberkulose und Boeckscher Krankheit, Folia haemat. **61**:345-352, 1939.

4. Schleicher, E. M.: Miliary Tuberculosis of the Bone Marrow, Am. Rev. Tuberc. **53**: 115-121, 1946.

5. Nickerson, D. A.: Boeck's Sarcoid: Report of 6 Cases in Which Autopsies Were Made, Arch. Path. **24**:19-29, 1937.

SUMMARY AND CONCLUSIONS

Lesions were found in the bone marrow in 9 of 24 patients with roentgenographic findings of diffusely distributed pulmonary lesions. Eight of the nine marrow lesions were granulomas. Several of the patients with normal marrow were later shown to have disease limited to the lungs.

The roentgenographic appearance of miliary opacities is of more importance in indicating marrow involvement than the presence of extensive lung involvement. Thus, no marrow lesions were found in the 25 patients with far-advanced pulmonary tuberculosis.

Examination of the marrow may be of diagnostic value in the presence of miliary opacities or diffusely distributed pulmonary lesions when disseminated granulomatous disease is suspected.

SECONDARY TUMORS OF HEART AND PERICARDIUM

Review of the Subject and Report of One Hundred Thirty-Seven Cases

MAJOR JAMES F. DeLOACH
AND
MAJOR JAMES W. HAYNES
MEDICAL CORPS, UNITED STATES AIR FORCE

HEKTOEN,[1] in 1893, while reporting two cases of secondary tumors of the heart, stated that 110 such cases had already been recorded. Despite this relatively impressive number and the numerous reports since that time, the recent literature contains references to the considered rarity of these tumors (Fischer,[2] Lymburner[3]). Several lengthy statistical reports on the subject have appeared in the literature since the turn of the century (Peters and Milne,[4] Morris,[5] Yater,[6] Hamilton,[7] Pollia and Gogol,[8] Scott and Garvin,[9] Lisa and associates,[10] Prichard[11]). Siegel and Young,[12] in 1933, reported 3 cases of metastatic tumors in 44 cases of

From the Cardiovascular-Renal Section (Major DeLoach) and the Pathology Section (Major Haynes), Walter Reed Army Hospital, Walter Reed Army Medical Center, Washington, D. C.

1. Hektoen, L.: Three Specimens of Tumors of the Heart: Metastatic Carcinomatous Nodule in the Myocardium; Implantation-Sarcoma of the Right Ventricle; Primary Round-Celled Sarcoma of the Epicardium, M. News **63**:571-574, 1893.

2. Fischer, J. W.: Neoplastic Involvement of Pericardium Producing the Syndrome of Constrictive Pericarditis, Am. Heart J. **35**:813-819 (May) 1948.

3. Lymburner, R. M.: Tumors of the Heart: Histopathological and Clinical Study, Canad. M. A. J. **30**:368-373 (April) 1934.

4. Peters, H. LeB., and Milne, L. S.: Secondary Tumors of the Heart, New York M. J. **94**:383-386, 1911.

5. Morris, L. M.: Metastases to the Heart from Malignant Tumors, Am. Heart J. **3**:219-229 (Dec.) 1927.

6. Yater, W. M.: Tumors of the Heart and Pericardium: Pathology, Symptomatology, and Report of 9 Cases, Arch. Int. Med. **48**:627-666 (Oct.) 1931.

7. Hamilton, R. L.: Metastatic Carcinoma of the Heart, Am. J. Cancer **16**:205-209 (Jan.) 1932.

8. Pollia, J. A., and Gogol, L. J.: Some Notes on Malignancies of the Heart, Am. J. Cancer **27**:329-333 (June) 1936.

9. Scott, R. W., and Garvin, C. F.: Tumors of the Heart and Pericardium, Am. Heart J. **17**:431-436 (April) 1939.

10. Lisa, J. R.; Hirschorn, L., and Hart, C. A.: Tumors of the Heart: Report of 4 Cases and Review of the Literature, Arch. Int. Med. **67**:91-113 (Jan.) 1941.

11. Prichard, R. W.: Tumors of the Heart: Review of the Subject and Report of 150 Cases, A. M. A. Arch. Path. **51**:98-128 (Jan.) 1951.

12. Siegel, M. L., and Young, A. M.: Electrocardiographic Findings in Tumors of the Heart: With a Report of a Case, Am. Heart J. **8**:682-690 (June) 1933.

malignant disease (7.4%) among 592 autopsies. Burke,[13] in 1934, in an analysis of 327 autopsies for malignant disease, observed 14 instances of metastatic involvement of cardiac muscle (4.3%). In the same year, Lymburner [3] noted 52 secondary tumors of the heart in a review of 8,550 autopsies at the Mayo Clinic (0.6% for all cases). Willis,[14] in 1934, in a review of 323 autopsies of patients with malignant tumors of all types, found metastatic growths in the myocardium in 20 cases (6.2%). In 1935, Helwig [15] noted nine instances of malignant invasion of the heart among 1,000 autopsies. Pollia and Gogol,[8] in 1936, noted 29 tumors of the heart occurring among 1,450 malignant tumors (2.0%) in 12,000 autopsies. Scott and Garvin,[9] in 1939, reported 118 instances of metastases to the heart and parietal pericardium in 1,082 cases (10.9%) of malignant tumors in 11,100 consecutive autopsies. This incidence represents the highest recorded prior to our report. Ritchie,[16] in 1941, reported 16 instances of secondary tumors in 857 deaths (1.8%) from malignant disease in 3,000 autopsies. In the same year, Lisa and associates [10] reported four cases of metastatic tumors of the heart, but did not indicate the number of autopsies from which the cases were drawn. Herbut and Maisel,[17] in 1942, reported 35 cases of secondary involvement of the heart in 640 deaths from malignant disease (5.4%) among 4,050 autopsies. Lefkovits,[18] in 1948, added six additional cases, but did not indicate the number of cases from among which his report was drawn. Dimmette,[19] in 1950, reported that 38 cases of metastatic tumors of the heart were observed in 455 cases (8.35%) of malignant disease in a review of 1,815 autopsies. In 1951, Prichard [11] recorded 146 cases of cardiac metastases among 4,375 autopsies for malignant diseases (3.4%), and in his excellent review, especially of primary tumors of the heart, stated that by 1950 more than 500 cases of secondary involvement of the heart had been recorded. His series includes the largest group of secondary tumors of the heart reported thus far. In the same year, Lamberta and associates [20] reported 31 cases of metastatic carcinoma of the pericardium in 1,032 cases of epithelial tumors (3%) among 6,257 autopsies.

From a brief review of the literature it appears that the heart is rarely directly involved by Hodgkin's disease (Wolpaw and associates,[21] Stout [22]). Garvin,[23] in

13. Burke, E. M.: Metastatic Tumors of the Heart, Am. J. Cancer **20**:33-47 (Jan.) 1934.

14. Willis, R. A.: The Spread of Tumors in the Human Body, London, J. & A. Churchill, Ltd., 1934.

15. Helwig, F. C.: Tumors of the Heart, J. Kansas M. Soc. **36**:265-272 (July) 1935.

16. Ritchie, G.: Metastatic Tumors of the Myocardium: Review of 16 Cases, Am. J. Path. **17**:483-489 (July) 1941.

17. Herbut, P. A., and Maisel, A. L.: Secondary Tumors of the Heart, Arch. Path. **34**:358-364 (Aug.) 1942.

18. Lefkovits, A. M.: Neoplastic Metastasis to the Heart, Am. Heart J. **36**:610-620 (Oct.) 1948.

19. Dimmette, R. M.: The Ante-Mortem Diagnosis of Secondary Tumors of the Heart: Report of 4 Cases, U. S. Armed Forces M. J. **1**:750-758 (July) 1950.

20. Lamberta, F.; Nareff, M. J., and Schwab, J.: Metastatic Carcinoma of the Pericardium, Dis. Chest **19**:528-536 (May) 1951.

21. Wolpaw, S. E.; Higley, C. S., and Hauser, H.: Intrathoracic Hodgkin's Disease, Am. J. Roentgenol. **52**:374-387 (Oct.) 1944.

22. Stout, A. P.: Human Cancer: Etiological Factors; Precancerous Lesions; Growth; Spread; Symptoms; Diagnosis; Prognosis; Principles of Treatment, Philadelphia, Lea & Febiger, 1932.

23. Garvin, C. F.: Hodgkin's Disease of the Heart and Pericardium, J. A. M. A. **117**:1876-1877 (Nov. 29) 1941.

1941, while reporting the first case of secondary involvement by Hodgkin's disease diagnosed ante mortem, credits Murchison [24] with recording, in 1869, the first case. Harrel,[25] in 1939, reviewed the eight recorded cases of Hodgkin's disease with pericardial lesions and reported the ninth case. McCoy,[26] in 1948, reported a case of Hodgkin's disease of the epicardium. Hagans,[27] in 1950, reported an unusual case of this disease in which the symptoms of pericarditis with effusion appeared several months prior to other subjective evidence of the underlying disease. Brick and Greenfield,[28] reporting from this hospital in 1947, stated that 10 cases of reticulum-cell sarcoma involving the heart had already appeared in the literature and added 2 more, 1 of which had been diagnosed ante mortem. Pilcher,[29] in 1950, recorded three cases of lymphosarcoma of the heart with an antemortem diagnosis in one case.

In a review of 2,547 consecutive autopsies at the Walter Reed Army Hospital covering an 11-year period ending in 1951 and including 980 cases of malignant disease, the over-all incidence of metastatic tumors of the heart and pericardium was 5.3%, and the incidence in cases of malignant disease was 13.9%. The main reason for the high proportion of autopsies for malignant disease is the fact that Walter Reed Army Hospital is a tumor center for the Army and more patients in a terminal state remain in the hospital, in contradistinction to many institutions from which such patients must of necessity be sent home. The incidence of macroscopic secondary tumors of the heart in cases of metastatic tumors in this series (13.9%) represents the highest occurrence reported thus far. Cases in which only microscopic aggregations of tumor cells were observed in tissue sections of the heart and pericardium are excluded from this report. The relatively high incidence in this series is not easily explained. Points of possible significance are the comparative youth of the majority of the patients and the marked preponderance of males in our series.

PATHOLOGIC OBSERVATIONS

The heart and pericardium are subject to metastasis from almost any primary malignant tumor. Morris,[5] Yater,[6] Burke,[13] and Scott and Garvin [9] listed numerous primary sites of almost every conceivable origin. The experience in this series reflects the myriad possible sources (Table 1). Cardiac involvement by metastases is usually multiple and part of a general dissemination of the primary tumor. Cases

24. Murchison, C.: Case of a New Morbid Growth, Composed of Muscular Tissue, in the Intestine, Liver, Kidneys, Lymphatic Glands, Heart, and Other Organs, Tr. Path. Soc. London **20**:192, 1869.

25. Harrel, G. T.: Hodgkin's Disease with Invasion of Pericardium and Gallbladder: Review of the Literature and Report of a Case with Autopsy, Arch. Path. **28**:58-64 (July) 1939.

26. McCoy, J. J.: Hodgkin's Disease Involving the Epicardium: Report of a Case, U. S. Nav. M. Bull. **48**:272-275 (March-April) 1948.

27. Hagans, J. A.: Hodgkin's Granuloma with Pericardial Effusion: Unusual Case of Hodgkin's Disease Presenting Initially Signs and Symptoms of Pericarditis with Effusion, Am. Heart J. **40**:624-629 (Oct.) 1950.

28. Brick, I. B., and Greenfield, M.: Reticulum Cell Sarcoma with Cardiac Metastasis: Report of Two Cases with Ante-Mortem Diagnosis of One, Am. Heart J. **34**:599-611 (Oct.) 1947.

29. Pilcher, R. B.: Lymphosarcoma Invading the Heart: A Report of 3 Cases with Autopsy Findings, M. J. Australia **2**:366-371 (Sept. 2) 1950.

of solitary metastasis to the heart are extremely rare. Herbut and Maisel [17] noted one instance in which a solitary metastasis to the left ventricle represented the only metastasis observed. The current series does not contain any case in which the heart was the sole site of metastasis. Lymburner [3] noted concurrent extracardiac intrathoracic malignant involvement in 88% of 52 cases of secondary tumors of the heart. He pointed out that the lung was involved by malignancy in 72% of these cases. Of the present series of 137 cases of cardiac metastases, in all but 1

TABLE 1.—*Distribution of 137 Secondary Tumors of Heart and Pericardium*

Primary Tumor	Total Cases	Metastasized to Pericardium	Metastasized to Heart	Metastasized to Heart and Pericardium	Metastasized to Pericardium, Heart, or Both
Carcinoma of bronchus	105	8	4	10	22
Carcinoma of breast	40	7	1	2	10
Carcinoma of kidney	20	0	1	0	2
Carcinoma of colon	12	0	1	1	1
Carcinoma of ovary	16	1	0	0	1
Carcinoma of nasopharynx	15	1	0	0	1
Carcinoma of bladder	19	1	0	1	2
Carcinoma of prostate	19	0	1	0	1
Carcinoma of parotid	3	0	1	0	1
Carcinoma of tongue	9	0	1	0	1
Embryonal ca. of testis	25	0	2	0	2
Choriocarcinoma of testis	12	0	2	0	2
Teratocarcinoma of mediastinum	1	0	1	0	1
Hodgkin's disease	19	0	2	1	3
Lymphosarcoma	33	0	5	9	14
Reticulum-cell sarcoma	15	2	10	6	18
Lymphatic leukemia	62	0	5	10	15
Malignant melanoma	22	0	4	9	13
Malignant myoblastoma	1	0	1	0	1
Adrenal neuroblastoma	1	0	1	0	1
Malignant mediastinal teratoma	1	0	0	1	1
Wilms's tumor	3	0	1	1	2
Hypernephroma	3	0	2	0	2
Fibrochondrosarcoma of ilium	1	0	1	0	1
Fibrosarcoma of leg	1	0	1	0	1
Fibrosarcoma of maxilla	1	0	1	0	1
Chondrosarcoma of ilium	1	0	1	0	1
Hemangioendothelial sarcoma (primary site undetermined)	1	0	1	0	1
Sarcoma, undifferentiated	2	2	0	0	2
Myelogenous leukemia	45	0	4	8	12
Miscellaneous *	384	0	0	0	0
Totals	980	22	56	59	137

* Denotes a number of various malignant tumors not observed as metastasizing to the heart or pericardium.

there was associated intrathoracic malignancy. Scott and Garvin [9] observed that carcinoma of the bronchus and breast were the more common primary sites of metastases to the heart and pericardium (35.6% each) in their series. Herbut and Maisel [17] reported a 12% incidence of involvement of the heart by secondary tumors from carcinoma of the lung. They indicated, however, that carcinoma of the lung, breast, esophagus, larynx, and small intestine metastasize to the heart with about equal frequency. Involvement of the pericardium by bronchogenic carcinoma has

been noted to vary from 2 to 26% (Jaffé,[30] Ochsner and DeBakey[31]). The incidence of pericardial metastases has been observed to vary from 4.52 to 18% (Warren and Witham,[32] Saphir and Parker[33]) in carcinoma of the breast and from 3 to 6% in cancer of the pancreas (Grauer,[34] Duff[35]). Scott and Garvin[9] noted involvement of the heart in over 50% of cases of reticulum-cell sarcoma, lymphatic leukemia, and malignant melanoma in their series. Yater[6] stated that carcinomatous metastases are more common than sarcomatous. Lymburner's[3] observations support this view.

Secondary tumors of the heart and pericardium usually reflect the histologic appearance of the primary tumor. Grossly they vary greatly in size, shape, and distribution. Cardiac enlargement and deformity depend upon both the extent and the distribution of involvement. Carcinomatous and sarcomatous metastases usually appear as discrete nodules, whereas leukemic infiltrations are more commonly diffuse. Metastases to heart valves are extremely rare. Coller and associates[36] in their review of the literature in 1950 noted only nine cases in which tumor depositions were seen on the endocardium; tumor nodules were implanted on the cardiac valves in six of these. They reported a 10th case, that of a metastatic bronchogenic carcinoma of the endocardium with implants on the tricuspid and mitral valves. They pointed out that valvular implants in all the six previously reported cases were limited to the tricuspid valve and stated that their case represented the first recorded instance of mitral-valve implantation. The six previous cases were instances of carcinomatous valvular implants.

The pericardium is not infrequently diffusely thickened or obliterated when involved by metastasis. In this series, pericardial spread was observed in 81 cases; diffuse thickening was noted in 16 and obliteration in 15. Secondary tumors may occupy entire heart chambers and even extend to other chambers (Case 1). Pericardial effusion is not uncommon in cases in which there is extensive pericardial involvement, especially those in which the pericardial cavity has not been obliterated. This effusion may be hemorrhagic and is characterized by rapid reappearance following pericardicentesis.

The right side of the heart is generally the more frequent site of metastasis (Yater,[6] Lymburner,[3] Prichard[11]). The distribution in this series also narrowly favored the right (Table 2). Scott and Garvin[9] and Burke[13] noted the converse

30. Jaffé, R. H.: Primary Carcinoma of the Lung: Review of 100 Autopsies, J. Lab. & Clin. Med. **20**:1227-1237 (Sept.) 1935.

31. Ochsner, A., and DeBakey, M.: Significance of Metastasis in Primary Carcinoma of the Lungs: Report of 2 Cases with Unusual Site of Metastasis, J. Thoracic Surg. **11**:357-387 (April) 1942.

32. Warren, S., and Witham, E.: Studies on Tumor Metastasis: Distribution of Metastases in Carcinoma of the Breast, Surg., Gynec. & Obst. **57**:81-85 (July) 1933.

33. Saphir, O., and Parker, M. L.: Metastasis of Primary Carcinoma of Breast, with Special Reference to Spleen, Adrenal Glands, and Ovaries, Arch. Surg. **42**:1003-1018 (June) 1941.

34. Grauer, F. W.: Pancreatic Carcinoma: Review of 34 Autopsies, Arch. Int. Med. **63**: 884-898 (May) 1939.

35. Duff, C. L.: Clinical and Pathological Features of Carcinoma of the Body and Tail of the Pancreas, Bull. Johns Hopkins Hosp. **65**:69-99 (July) 1939.

36. Coller, F. C.; Inkley, J. J., and Moragues, V.: Neoplastic Endocardial Implants: Report of a Case, Am. J. Clin. Path. **20**:159-164 (Feb.) 1950.

in their series. Morris [5] and Herbut and Maisel [17] observed an equal distribution between the two sides. Tumors may spread to the heart by direct extension or by invasion of the systemic veins, pulmonary veins, or lymphatics. The tumor having invaded one or more of these vessels, intraluminal fragments of tumor may become detached and be transported to the heart, or the malignant cells may grow by continuous extension along the vena cava, pulmonary veins, or lymphatics. In lymphatic spread, the neoplasm may reach the heart via the systemic veins or by retrograde extension up the cardiac lymphatics. The mode or combination of modes of metastases depend on the site and character of the primary tumor. The chondrosarcoma in Case 1 and one of the three Wilms tumors in this series coursed to the right atrium by continuous growth up the lumen of the inferior vena cava. This mechanism of extension is not uncommon in Wilms's tumor and chondrosarcoma. The embolic transfer of tumor cells from their primary site to the heart and pericardium is generally accepted as the most common mode of metastasis (Yater,[6] Willis,[14] Scott and Garvin [9]). This method does not explain the predilection for involvement of the right side of the heart. In fact, only the rarest of cardiac metastases, the endo-

TABLE 2.—*Sites of Secondary Tumors* of the Heart in 137 Cases*

Right atrium	55
Right ventricle	63
Left atrium	47
Left ventricle	60
Right side of heart	118
Left side of heart	107
Interatrial septum	29
Interventricular septum	42

* All secondary tumors were macroscopic; there were no microscopic aggregations of tumor cells regarded as "tumors" in this series.

cardial implants, may be quickly dismissed as problematical in their mode of arrival to the right side. Yater [6] credits Windholz [37] with cleverly employing the work of Kretz [38] to explain the incongruous predilection. Kretz [38] noted that approximately 75% of a solution injected into the coronary arteries was returned to the right chambers of the heart after passing through the thebesian and coronary veins. The meager blood supply of the cardiac valves readily explains their immunity to secondary involvement except for rare cases of implantation (Coller and associates,[36] Yater [6]). Harrel [25] cited the several intricate routes of lymphatic channels between the heart, pericardium, and mediastinal nodes as detailed by Rouvière [39] and concluded that the pericardium could be reached by any of these avenues. Prichard,[11] in his series, noted that the lymphatic route was followed more frequently than the route of direct invasion even in his cases of carcinoma of the lung. It is generally agreed that lymphatic spread to heart and pericardium is of necessity by retrograde movement from the tracheobronchial lymph nodes which drain the myocardium and pericardium.

37. Windholz: Über Thromben und Geschwülste des Herzens, Arch. path. Anat. **273**:331-366, 1929.

38. Kretz, J.: Über die Bedeutung der Venae minimae Thebesii für die Blutversorgung des Herzmuskels, Arch. path. Anat. **266**:647-675, 1928.

39. Rouvière, H.: Anatomie des lymphatiques de l'homme, Paris, Masson & Cie, 1932.

Scott and Garvin [9] noted that direct extension from either a primary or a secondary malignant disease of the lungs or secondary tumor of the mediastinal lymph nodes was the second most common route of metastasis. Direct extension is generally the less frequent mode of metastasis. Willis [14] divides direct invasion into "contact metastasis" wherein there is an apposition of structures, and "direct metastasis," whereby metastasis follows the direction of blood or lymph flow. The term "paradoxic metastasis" (retrograde) is reserved for that form by which direct invasion proceeds upstream to the flow within blood or lymph channels. This route is more common to primary tumors of the lung, esophagus, or mediastinum and to metastatic tumors of intrathoracic lymph nodes. Yater [6] cites unusual examples of direct extension, such as invasion of the left upper pulmonary vein with extension into the left auricle. In this series the frequency of the various modes of spread favored the embolic pathways (Table 3). In 42 cases the tumor traveled to the heart by a combined blood stream and lymphatic route. Obviously, a metastasis may reach a locale nearer the heart by one method and later complete its trip to the

TABLE 3.—*Frequency of Various Modes of Involvement of Heart and Parietal Pericardium by Secondary Tumors*

	Blood Stream	Blood Stream and Lymphatics Combined	Lymphatics	Direct Invasion
Carcinoma	9 (20%)	9 (20%)	10 (21%)	18 (39%)
Sarcoma	6 (75%)	0	0	2 (25%)
Lymphoma	18 (35%)	33 (65%)	0	0
Myelogenous leukemia	12 (100%)	0	0	0
Miscellaneous tumors	18 (90%)	0	0	2 (10%)
Totals	63	42	10	22

heart or pericardium via another more convenient route. The employment of all three modes of metastasis by tumor cells in traveling from their primary site to an ultimate goal in the heart or pericardium is conceivable.

CLINICAL OBSERVATIONS

Several authors have attempted to establish certain classifications of signs and symptoms that would aid in the antemortem diagnosis of these secondary tumors (Yater,[6] Fishberg,[40] Lisa and associates [10]). Yater [6] divided the symptomatology into two types, the first being poorly suggestive of the actual nature of the underlying disorder and the second being more definitely suggestive of neoplastic involvement. With the former, the patients are candidates for sudden inexplicable congestive failure, subacute bacterial endocarditis, or, more rarely, a sudden death usually not preceded by cardiac symptoms. The latter type of symptomatology may be expressed in a disturbance of cardiac rhythm, congestive heart failure in the presence of known malignancy, simple pericardial effusion or the hemorrhagic variety, and, more specifically, the sign of relative immobility of the right border of the heart as demonstrated by fluoroscopy. Yater emphasized that for patients with known malignant but without previous heart disease, a diagnosis of cardiac metastases should

40. Fishberg, A. M.: Auricular Fibrillation and Flutter in Metastatic Growths of the Right Auricle, Am. J. M. Sc. **180**:629-634 (Nov.) 1930.

be considered if an arrhythmia develops. Scott and Garvin [9] observed seven cases of cardiac failure caused by metastases to the heart, and diagnosed one case ante mortem. They concluded that the most important clinical finding pointing to cardiac metastasis is the development of cardiac failure in patients with known malignant disease but without any other basis for an incompetent heart. Wallace and Logue [41] have indicated the possible role of metastatic disease of the pericardium in producing the syndrome of constrictive pericarditis with resultant right-sided heart failure in patients with known malignant disease and without other obvious cause for such failure. Slater and associates,[42] in a recent report of a case of constrictive pericarditis caused by carcinosis arising from a primary carcinoma of the breast resected 14 years previously, noted electrocardiographic changes of acute pericardial injury (RS-T and T wave changes). They suggested that these changes, which are indicative of acute pericardial injury during the course of constrictive pericarditis, should lead to the suspicion of an active infectious or neoplastic pericardial process.

Lefkovits [18] stressed the importance of tachycardia as a possible sign of cardiac metastasis in patients having no known cause for this finding. Rosenbaum and

TABLE 4.—*Incidence of Involvement of Heart and Pericardium in 980 Cases of Malignant Disease*

	No. of Cases	% of 980 Cases of Malignant Disease
Heart	56	5.7
Parietal pericardium	22	2.2
Both heart and parietal pericardium	59	6.0
Heart or parietal pericardium or both	137	13.9

associates,[43] in reporting a case of metastatic carcinoma of the heart with production of RS-T segment elevations for over two months, concluded that the continued displacements in several leads were caused by injury to the myocardium by tumor. They indicated the nonspecificity of electrocardiographic changes produced by tumors of the heart and cited the similar experiences of others (Scott and Garvin,[9] Siegel and Young [12]). Siegel and Young, in an attempt to differentiate between electrocardiographic changes produced by coronary disease and metastases to the heart, noted the lack of reciprocal direction of T waves in Leads I and III and the failure to manifest S-T segment displacement as observed in their case of metastatic reticulum-cell sarcoma of the heart.

In summary, the development of congestive failure that is refractive to accepted therapy, dyspnea, arrhythmia, cardiomegaly, simple or hemorrhagic pericardial effusion, distant heart sounds, signs of superior vena cava obstruction, inexplicable tachycardia, pericardial friction rub or other evidence of constrictive pericarditis,

41. Wallace, J. J., and Logue, R. B.: Metastatic Carcinoma as a Cause of Constrictive Pericarditis: Report of a Case, Am. Heart J. **31**:223-230 (Feb.) 1946.

42. Slater, S. R.; Kroop, I. G., and Zuckerman, S.: Constrictive Pericarditis Caused by Solitary Metastatic Carcinosis of the Pericardium and Complicated by Radiation Fibrosis of the Mediastinum, Am. Heart J. **43**:401-412 (March) 1952.

43. Rosenbaum, F. F.; Johnston, F. D., and Alzamora, V. V.: Persistent Displacement of the RS-T Segment in a Case of Metastatic Tumor of the Heart, Am. Heart J. **27**:667-675 (May) 1944.

radiologic evidence of an irregular or unusual heart border, or relative immobility of the right border of the heart on fluoroscopy, should arouse suspicion of cardiac metastasis if the more common causes for these signs and symptoms can be reasonably excluded. Electrocardiograms were made in 38 of the cases in this series. Twenty-two of the tracings were interpreted as having abnormalities, of which five were attributed to possible metastatic involvement of the heart. In this series there were only two cases in which signs of myocardial insufficiency developed. These were not suspected clinically of being due to extensive tumor involvement of the myocardium, as was demonstrated post mortem. In two other cases there was clinical and roentgen evidence of cardiac tamponade, autopsy showing massive hemorrhagic pericardial effusion secondary to pericardial metastases. Cardiomegaly was demonstrated by roentgen study in 17 cases. In none of the 16 cases in this series in which there was simple pericardial effusion were there signs or symptoms ante mortem. Of the six cases of hemorrhagic pericardial effusion, there was clinical evidence of pericardial effusion in only two. In only two cases was the development of distant heart sounds recorded. Superior vena cava obstruction was noted in two cases. In only two cases was there an inexplicable tachycardia. A pericardial friction rub developed late in two cases. In only one case was an irregular heart border noted on roentgen examination. Electrocardiograms showed arrhythmias in five cases, S-T segment displacement and abnormal T waves in nine cases, and a left bundle branch block in one case; a sinus tachycardia was present in seven cases. These electrocardiographic abnormalities were found in young adults except in two cases in which the changes could be attributed to arteriosclerotic heart disease as well as to tumor. Abnormal cardiac signs were noted physically in 23 of the cases; however, in only 7 instances were the signs interpreted as evidence of possible or probable cardiac metastasis.

The difficulty of diagnosing ante mortem the secondary involvement of the heart or pericardium by a malignant process is reflected in the fact that of the more than 500 such cases reported by 1950 (Prichard [11]), in only 21 had the diagnosis been made ante mortem (Dimmette [19]). (Four primary tumors of the heart have been diagnosed ante mortem, bringing the total cases in which the diagnosis was made ante mortem to 25.) The first antemortem diagnosis of the secondary tumor of the heart was reported by Rösler [44] in 1924 (sarcoma of the cheek). Doane and Pressman,[45] reporting in 1942 the 20th case of tumor of the heart diagnosed ante mortem, stated that in the 12 years since Fishberg,[40] in 1930, had reported three other tumors diagnosed ante mortem, 12 cases had been observed and reported by American authors. Brick and Greenfield,[28] reporting from this hospital in 1947, recorded two cases of reticulum-cell sarcoma involving the heart and pericardium. An antemortem diagnosis was made in one of these cases. In our series a definite clinical diagnosis of metastatic invasion of the heart was made in three cases, one of which has been reported in detail (Brick and Greenfield [28]); another case is awaiting publication (Hall [46]). The third case is appended in detail (Case 2).

44. Rösler, O. A.: Vier seltenere Herzbefunde, ein Beitrag zur Herz Diagnostik, Zentralbl. Herz-u. Gefässkr. **16**:261, 1924.

45. Doane, J. C., and Pressman, R.: Ante-Mortem Diagnosis of Tumors of the Heart, Am. J. M. Sc. **203**:520-524 (April) 1942.

46. Hall, R. J.: Unpublished data.

TREATMENT

Although it is absurd at this time to attempt a discussion of a cure for metastatic or primary malignant disease of heart or pericardium, it is important that physicians diagnose or suspect such involvement of these structures. Considerable amelioration of severe pain or discomfort and increased survival may be offered to patients with cardiac metastasis. This fact was first indicated by Shelburne and Aronson,[47] in 1940, when they produced remission of a metastatic tumor of the heart involving the pericardium and bundle of His causing complete heart block. After high-voltage roentgen therapy to the heart area, pericardial effusion disappeared, and normal cardiac mechanism was reestablished. The patient died several months later of mediastinal compression, but no signs of recurrence of cardiac involvement were observed after roentgen therapy that apparently had no untoward effect upon function of the heart. Levy [48] suggested that the new discoveries in the employment of isotopes may further enhance the physician's ability to alleviate symptoms in these patients.

SUMMARY

In a series of 2,547 consecutive autopsies performed at the Walter Reed Army Hospital during the past 11 years, a total of 980 cases of malignant disease were observed. The heart, including the pericardium, was the site of metastatic tumor in 137 cases, an incidence of 13.9%. Carcinoma of the lung invaded the heart and pericardium more frequently than did other malignant processes, with a rate of 21% of 105 cases. Lymphatic leukemia invaded macroscopically in approximately the same percentage, but the case total was only 62. An antemortem diagnosis was made in three cases in this series, one of which has been reported in detail; the second awaits publication. Case 2 in the appended detailed case reports represents the third such case.

Five cases in which there were significant clinical, laboratory, or necropsy findings are reported below in detail.

CONCLUSIONS

Secondary tumors of the heart or pericardium are not rare in persons dying of malignant disease. No simple explanation is advanced for the relatively high incidence of secondary involvement of the heart and pericardium in this series. Of possible significance is the fact that the patients were preponderantly young men.

It is important that the physician carefully interpret cardiac signs and symptoms or electrocardiographic abnormalities in patients with malignant disease in order to avoid overlooking possible metastasis to the heart or pericardium. Antemortem diagnosis of such involvement may provide a more specific basis for ameliorative therapy.

REPORT OF CASES

CASE 1.—*Chondrosarcoma of the right ilium with metastases to the heart, right lung, inferior vena cava, mesenteric veins, hepatic vein, iliac veins, and the right renal and adrenal veins.*

47. Shelburne, S. A., and Aronson, H. S.: Tumors of the Heart: Report of a Secondary Tumor of Heart Involving Pericardium and Bundle of His with Remission Following Deep Roentgen-Ray Therapy, Ann. Int. Med. **14**:728-763 (Oct.) 1940.

48. Levy, T.: Metastatic Malignancies Involving the Heart, Postgrad. Med. **5**:407-411 (May) 1949.

A white woman, married, aged 26, was admitted to the Walter Reed Army Hospital on May 7, 1946, complaining of painful swelling and erythema of her right lower extremity. The present illness began one week prior to admission and was manifested initially by painful swelling in the right popliteal area, gradually involving the entire limb. There was no history of a previous similar episode. Her past medical history, aside from a normal term delivery of a viable fetus three weeks prior to admission, was of no significance. System review revealed a history of an uncomplicated appendicitis three years earlier and considerable menstrual irregularities since the menarche, at age 17. Her habits were not unusual. Except for her mother's death as a result of carcinoma of the uterus, the family history was not significant.

Relevant physical findings were a diffuse reticular cyanosis of the entire right lower extremity, mild pretibial pitting edema on the right, and exquisite tenderness and hyperesthesia of the right groin and right lower abdominal quadrant. Homan's sign was positive, and calf tenderness was present in the right leg. A complete blood count, urinalysis, and tests of bleeding, clotting, and prothrombin times gave normal results. The sedimentation rate was 42 mm. an hour. On May 26, a roentgenogram of the chest was normal.

The patient was treated with strict bed rest, elevation of and local heat to the affected limb, intragluteal injections of procaine penicillin, and a series of lumbar sympathetic (procaine) blocks which afforded complete temporary relief from pain. However, several days after admission, she complained of a small painful mass in the right buttock; examination showed a soft, tender, painful walnut-sized mass. This was ascribed to penicillin injections, and no further attention was given the lesion. After hospitalization for one month there was satisfactory improvement of the affected limb, and she was discharged with a final diagnosis of severe acute thrombophlebitis, secondary to term pregnancy.

The patient was readmitted to this hospital on Aug. 16, complaining of continued dull ache in her right thigh, accompanied by gradual enlargement and induration of the original mass in the right buttock. Her pain caused much insomnia, but, strangely, neither passive nor active movement of her right lower extremity evoked any accentuation of pain in the buttock. Physical examination upon readmission revealed a tender, mobile, poorly circumscribed mass posterior to the right trochanteric area. Dependent edema of the right lower extremity was noted. Physical findings otherwise were normal. A complete blood count and urinalysis gave normal results, and the values for blood calcium and alkaline phosphatase were normal. Multiple-view roentgenograms of the bony pelvis provided the first evidence of the seriousness of the patient's illness by disclosing advanced destructive changes in the right transverse processes of the first and second sacral segments and a portion of the right ilium adjacent to the sacroiliac joint. Above the sacroiliac joint were noted irregular calcific deposits extending over a 2.5 by 4.0 cm. area, with sclerotic changes in the bone adjacent to the right sacroiliac joint. On Aug. 19, biopsy of the tumor in the right buttock revealed a chondrosarcoma. At operation the tumor was observed to extend superiorly and posteriorly from the crest of the ilium to invade all surrounding muscles. The tumor was extremely vascular and bled readily upon manipulation.

During September a course of high-voltage radiation, a total tumor dose of 5,234 r, was delivered to the tumor area. A roentgenogram of the chest revealed no evidence of metastasis or other abnormality. The patient was discharged from the hospital on Oct. 1. Apparent improvement lasted for only a few weeks, and in December she noted a painful mass over the right ischial tuberosity. In January, 1947, a second course of high-voltage roentgen therapy brought the total tumor dosage to 9,194 r. In March and May her progress was regarded as satisfactory; roentgenograms of the tumor area at those times revealed marked increase in calcification. In September she initially noted pain in the lower lumbar and right posterior pelvic areas. Roentgenograms of the chest were again normal; those of the pelvis remained unchanged.

On Oct. 5, she was seen as an outpatient at another hospital for a complaint of right pleural pain. Her temperature was 101 F., and a roentgenogram of the chest was normal, but another film several days later revealed a pleuritic reaction in the left lung base. Fluoroscopy, several days later, revealed obliteration of the left costovertebral angle. On Oct. 30, she was admitted to that hospital in a nearly prostrate condition. Physical examination revealed a temperature of 96.4 F.; pulse regular, at 60, and respirations, 18. She was acutely distressed and appeared chronically ill. Diffuse rales were heard inferiorly in the left side of the chest, with some roughening of the inspiratory note. No signs of frank pulmonary consolidation were found. No heart

murmurs were heard, but percussion suggested slight generalized enlargement of the heart. No abnormal findings were elicited on abdominal examination. The area over the right iliac crest anteriorly was tender, but no masses were palpated. Results of the remainder of the examination were regarded as normal.

Laboratory studies revealed a slight anemia. A urine specimen obtained by catheterization showed a 1+ reaction for albumin. Roentgenograms of the pelvis (Fig. 1) demonstrated a large tumor, measuring 11.2 by 13 cm., interpreted as arising from the right aspect of the sacrum and projecting above the right ilium. The tumor contained dense new bone formations of mottled character throughout; its surface was slightly irregular. Bone formation was more pronounced near the central portion of the tumor. Roentgenographic survey of the skeleton revealed no evidence of local or distant metastases.

Prostration continued, and persistent vomiting ensued. Supportive therapy was of no avail. Inexplicably, on Nov. 1, she began to have what was interpreted as her first menses since September, 1946. By Nov. 2, she became confused and violent and was transferred to the Walter Reed Army Hospital.

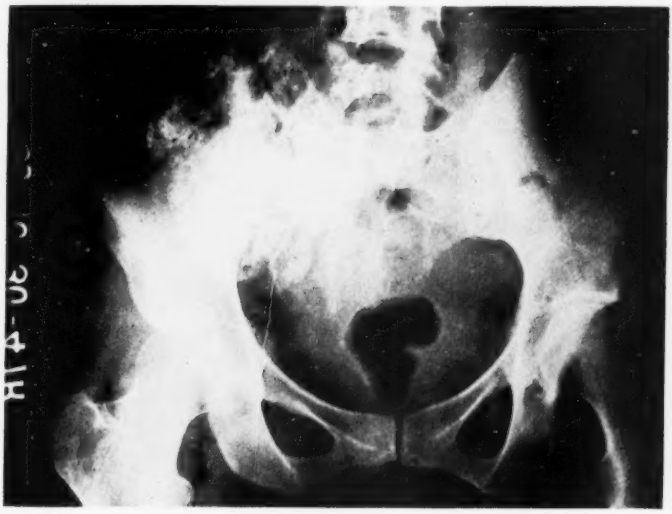


Fig. 1 (Case 1).—Chondrosarcoma of right ilium. Roentgenogram showing large tumor appearing to arise from right aspect of the sacrum and adjacent ilium.

Physical examination revealed confusion, mild icterus, dilated but reactive pupils, and normal fundi. Relative dullness was noted over both lung bases posteriorly. The heart was normal to percussion and auscultation and the blood pressure 100/56. The abdomen was markedly distended, and the liver edge extended 3 fingerbreadths below the right costal margin; however, no ascites was detected. All deep tendon reflexes were normal. A tourniquet test was positive. Blood urea nitrogen and carbon dioxide-combining power were normal. A urine specimen gave a 4+ reaction for albumin; 10 to 12 erythrocytes and a few granular casts were seen on microscopic examination. A sample of gastric secretions gave a 4+ reaction for occult blood. Despite supportive measures the patient died one day after admission.

Pertinent Necropsy Observations.—There were 750 and 600 cc. of clear amber fluid in the right and left pleural cavities, respectively. The pleural surfaces were smooth. Both lung bases were atelectatic; a minute metastatic nodule was found in the upper lobe of the right lung. The pericardial sac contained 30 cc. of pale-amber fluid. Upon dissection of the great vessels, a large mass which resembled a "chicken-fat" thrombus was encountered in the inferior vena cava.

However, on inspection the mass resembled tumor tissue and extended up the inferior vena cava into the right atrium, attaching itself to the posterior aspect of the interatrial septum in an area 0.6 cm. in diameter. Elsewhere the tumor was free, a portion extending down into the apex of the right ventricle and terminating in a rounded end. No processes extended into the pulmonary artery. Surfaces of the tumor in the heart chambers resembled a diminutive brain, being composed of wrinkled convolutions of uniform yellow, translucent, rubbery material (Fig. 2). On cut surface, the tumor contained rounded nodules and whorled masses. The endocardium in all other chambers appeared normal and delicate; all valves were competent. The myocardium was of normal, moderately firm tone and reddish brown. The heart weighed 235 gm. and from its external appearance did not manifest enlargement in situ. Muscle thicknesses of

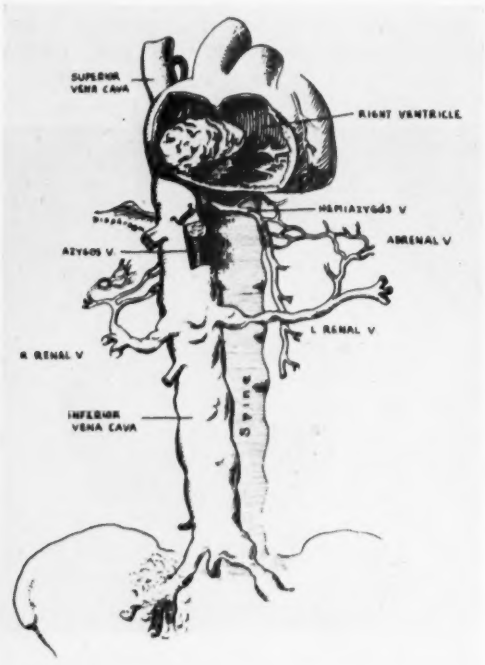


Fig. 2 (Case 1).—Chondrosarcoma of right ilium. Drawing depicting bulging of inferior vena cava and its radicles by tumor extending from region of ilium upward into right auricle and ventricle.

the right and left ventricular bases were 0.2 and 1.6 cm., respectively. The tumor in the right side of the heart appeared only slightly constricted as it entered the tricuspid opening. It was noted that the coronary ostia were patent and the vessel walls soft, and no occlusions were present. The vena cava was completely filled from a point below the junction of the iliac veins up to, and into, the heart by a mass of yellow tumor. Dissection through the upper abdominal segment of the vena cava, distended to a diameter of 4.2 cm., showed it to be filled with grayish-yellow rubbery fibers containing numerous spicules of gritty whitish material. Descending along the right iliac vein, the tumor invaded the lumen to the level of the lower border of the right sacroiliac joint; here the vein became incorporated in the main tumor mass. The tumor was intimately adherent to the vena cava lining at all points up to its entrance into the heart, and it invaded the hepatic, mesenteric, right renal, and right adrenal veins for short distances.

The hemiazygos vein distended increasingly cephalad; the azygos vein was compressed by the crossing of the hemiazygos. The right renal vein was occluded for a distance of 2 cm. beginning 1.5 cm. from the vena cava. The vein distal to the occlusion was moderately distended. Four small veins were noted draining the right kidney into the compressed azygos vein. No abnormalities of the portal vein were seen. The left common iliac vein was patent to 2 cm. from the vena cava; here it was collapsed with adhesions of its intima. The mass in the pelvis consisted of hard cartilaginous tumor arising from the posterior-medial portion of the ala of the right ilium adjacent to the sacrum and extending 3 cm. cephalad of the iliac crest. The tumor was bound down to the adjacent soft tissues by dense fibrous connective tissue.

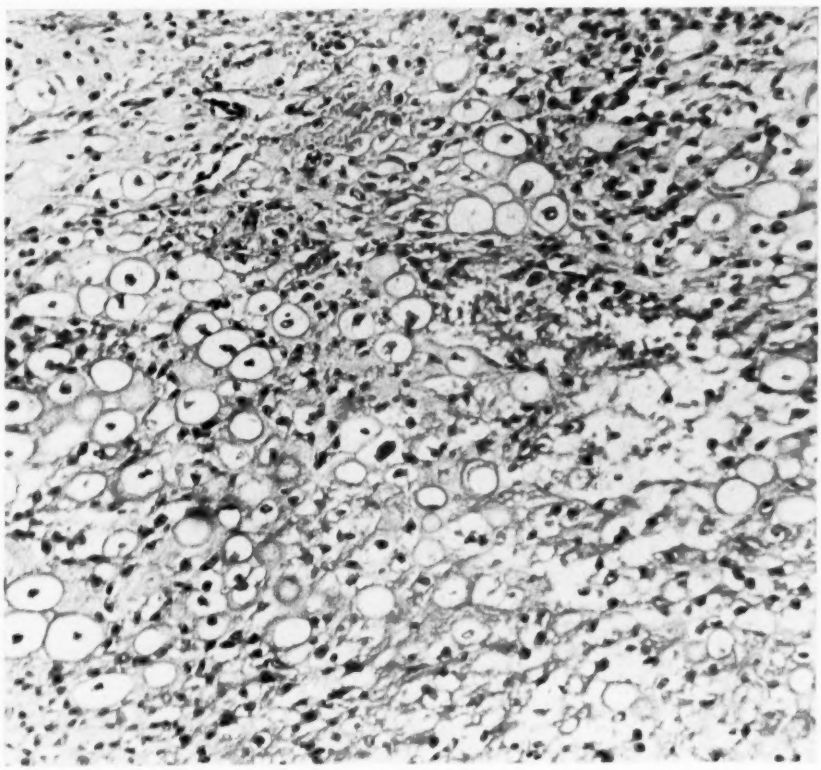


Fig. 3 (Case 1).—Chondrosarcmoa of right ilium. Low-power view of tumor. Note pleomorphic neoplastic cartilage cells irregularly placed in cartilage matrix. × 100.

Microscopically, the tumor tissue in its original site and in the metastases showed moderately well differentiated chondrosarcoma with masses of basophilic matrix containing numerous lacunar spaces occupied by neoplastic cartilage cells. These cells had eosinophilic cytoplasm, and one, or occasionally two, small round nuclei. In some areas the cells tended to line up in columns (Fig. 3). Sections of the heart did not show invasion of the wall proper by the tumor, which was adherent to the endocardium in the areas observed grossly. Other relevant observations were a centrolobular hepatic necrosis secondary to occlusion of the hepatic vein and a metastasis in the right adrenal.

Comment.—During the course of the patient's illness, there were no findings to arouse suspicion of invasion of the heart by tumor. No electrocardiograms were made.

Case 2.—*Hemangioendothelial sarcoma, original site undetermined, involving the heart, liver, brain, left adrenal, left third and right fifth ribs, right humerus, left clavicle, and fourth lumbar vertebra.*

A white man aged 46 was admitted to Walter Reed Army Hospital on Oct. 26, 1949, complaining of shortness of breath and substernal pain on exertion. He had been well until June 4, at which time, while swimming, he noted these symptoms. After a few minutes' rest, a resumption of swimming resulted in a severe exacerbation of pain and dyspnea. Four days later he was admitted to an army hospital on Guam, and a diagnosis of virus pneumonia was made. One week later a precordial friction rub was heard and interpreted as being due to pericarditis. On July 14, he was transferred to an army hospital in the United States, where his persistent low-grade temperature returned to normal following aureomycin and streptomycin therapy. In early October an aching pain developed in the right side of his thorax; a diagnosis of constrictive pericarditis was made, and he was transferred to the Walter Reed Army Hospital for possible surgical intervention. Family history, past medical history, and habits were not significant.

Physical examination revealed a chronically ill patient in no acute distress. There was a striking distention of neck veins and a purplish hue to his face. Examination of his chest elicited

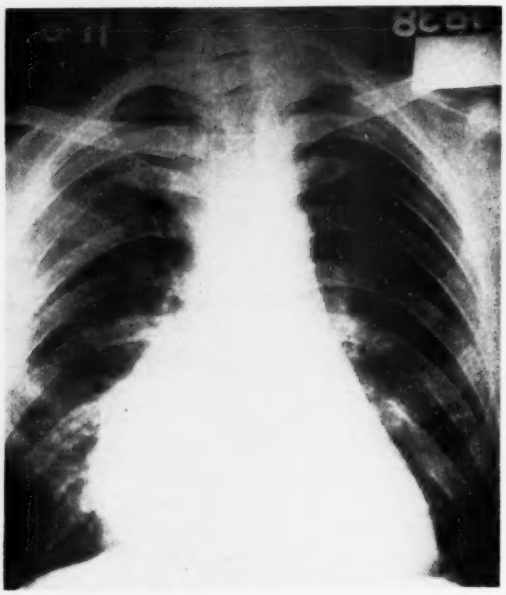


Fig. 4 (Case 2).—Hemangioendothelial sarcoma. Roentgenogram of chest showing large mass continuous with right border of heart. Note erosion of right fifth rib posteriorly and homogeneous density in lateral aspect of right upper chest opposite axilla.

increased vocal and tactile fremitus over the upper lobe of the right lung; a "leathery" squeaking rale was heard over this area on inspiration. There were no remarkable cardiac signs. The liver edge was nontender and extended 3 fingerbreadths below the right costal margin. The veins of the upper extremities were moderately distended.

After admission, a routine complete blood count and urinalysis gave normal results. A roentgenogram of the chest (Fig. 4) demonstrated clear lung fields and diaphragmatic contours. The right border of the heart was enl rged by the presence of a mass which was continuous with the heart shadow on the right and became convex laterally, was sharply defined, and measured approximately 8.5 by 4.0 cm. The right fifth rib posteriorly appeared eroded; a homogenous density in the axillary region of the chest was interpreted as pleural thickening. In October, an electrocardiogram was normal. A marrow biopsy of the sixth rib resulted in negative routine smears and culture; an acid-fast culture was also negative. The patient appeared to improve for a short while, but by December he began to fail rapidly. High-voltage roentgen irradiation had no effect on the size of the mediastinal mass. A biopsy of the right fifth rib posteriorly

in early December was interpreted as "sclerosing hemangioma." Bronchoscopic examination disclosed no abnormality; no neoplastic cells were obtained by bronchial washings. An angiogram several days later was unsuccessful. A liver biopsy in mid-December was interpreted as showing moderate fatty metamorphosis and portal fibrosis. Repetition of a biopsy of the fifth rib posteriorly in late December was interpreted as revealing fibrosarcoma. Roentgen therapy was reinstituted at this time. Coma developed on Jan. 17, 1950, and the patient died one week later.

Pertinent Necropsy Observations.—The right pleural cavity contained 450 cc. of blood-tinged fluid; no abnormalities of the pleurae were noted. The lower lobe of the left lung was bound to the thoracic cage by adhesions. There was no pleural effusion on the left. A cylindrical mass, measuring 3 cm. in diameter, occupied the right fifth rib from its vertebral articulation to the posterior axillary line. It was firm and covered by smooth pleura. On section, it had a dark red hemorrhagic appearance, in which there was firmer white tissue. It was gritty, and the tumor invaded the right third and fourth ribs. The left third rib was involved by a similar small mass.

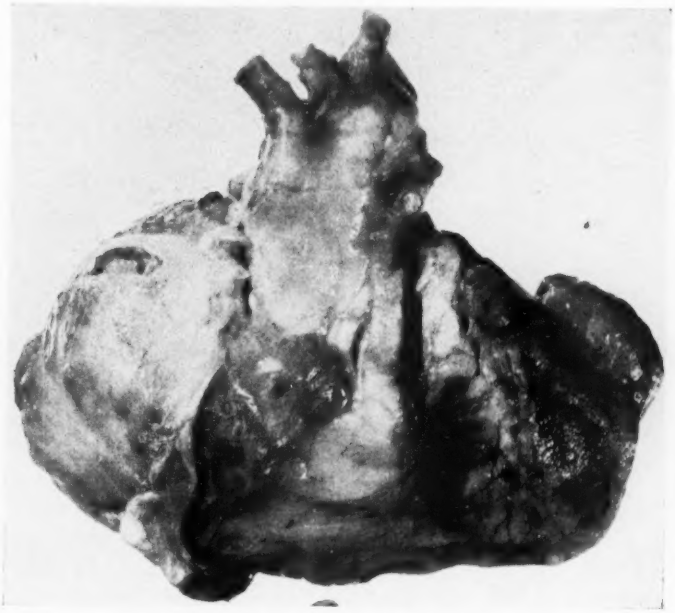


Fig. 5 (Case 2).—Hemangioendothelial sarcoma. Anterosuperior view of heart. Note large tumor mass involving right auricle and ventricle, tumor nodule attached to lateral aspect of left ventricle superior to apex, and tumor nodule overlying descending branch of left coronary artery.

The pericardium was firmly bound to the epicardium by fibrinous adhesions; the epicardium had a gelatinous appearance. Attached to the lateral surface of the left ventricle above the apex was a gelatinous, red, hemorrhagic tumor measuring 4.5 by 4 by 3 cm., intimately bound to the heart and attached to both the epicardium and the pericardium. Over the base of the heart and attached to the epicardium at the base of the pulmonary artery anteriorly was a tumor measuring 2 by 1.5 by 1 cm. Upon removal of the pericardium from the right side of the heart, a firm nodular mass measuring 9 by 9 by 7 cm. was encountered; it appeared to be confluent with, and part of, the wall of the right auricle. It had become intimately attached to the pericardium and had incorporated the epicardium in its growth. The surface of the mass was gray and glistening (Fig. 5). Upon opening of the right auricle, the orifice of the superior vena cava was markedly constricted by tumor; the inferior vena cava opened into the right auricle through a normal channel. The right auricular cavity was greatly reduced; tumor bulged into its antero-

superior portion. Numerous tumor nodules bulged from beneath the endocardial surface of the entire heart. Just above the anterior cusp of the tricuspid valve was a tumor formation measuring 4 by 4 cm. bulging into the auricular cavity (Fig. 6). The tumor involving the right auricle extended into the epicardial surface overlying the base of the aorta and invaded a portion of the base of the right ventricle. All the valve leaflets were delicate and the valves patent. Overlying the descending branch of the left coronary artery was a tumor measuring 2 by 1.5 cm. The left auricle was not remarkable. On cut section, the tumors were white and fibrous with scattered small hemorrhagic areas. The coronary arteries were grossly normal. Microscopically, sections from the various tumor sites all showed a similar appearance. The tumor consisted of spindle-shaped cells with eosinophilic cytoplasm having indefinite borders and oval-to-fusiform, moderately hyperchromatic nuclei; these cells lined vascular spaces in some areas and in others they

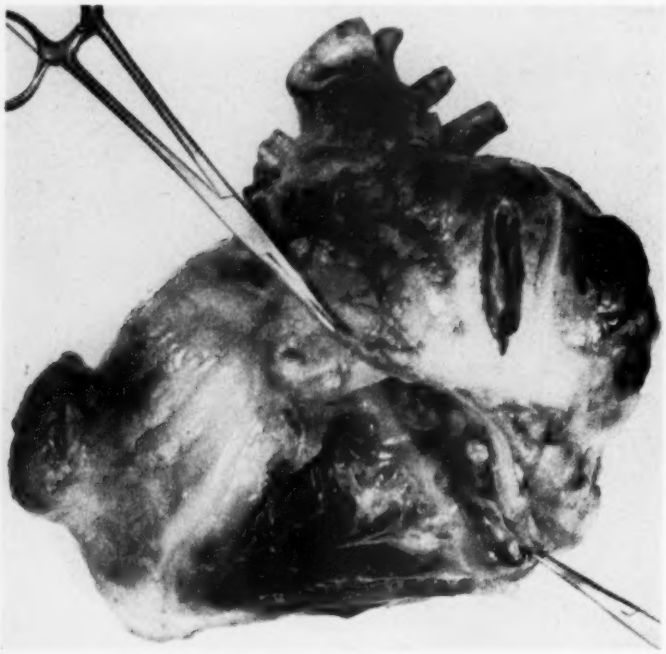


Fig. 6 (Case 2).—Hemangioendothelial sarcoma. Posteroinferior view of heart showing massive involvement of right auricle and base of heart by tumor. Note endocardial nodules in right auricle and marked compromise of lumen of right auricle.

lined up in bundles and appeared to be producing collagen. Mitotic figures were infrequent. There was extensive invasion at the borders in all sections, and many areas of hemorrhage and necrosis were seen. The tumor was interpreted as hemangioendothelial sarcoma (Figs. 7 and 8).

Comment.—Despite the clinical course and meticulous appraisal of necropsy observations, it was impossible to establish definitely the primary site of tumor. The clinical course at the onset suggested a pericarditis followed by constrictive pericarditis. Later, roentgenograms of the chest revealed massive involvement of the right side of the heart by tumor. Periodic electrocardiograms revealed no significant abnormalities.

CASE 3.—*Malignant melanoma, primary site unknown, with widespread metastases involving heart, pericardium, pleura, lungs, spleen, liver, kidneys, brain, and lymph nodes.*

A white man aged 27 was admitted to an army hospital on March 15, 1946, complaining of a painless, freely movable mass of golf-ball size in his left axilla. There were no other symptoms,

and physical examination revealed no other abnormalities. The mass was removed and showed malignant melanoma metastatic in lymph nodes. Review of past medical and family history and habits revealed nothing of significance. After biopsy, he was transferred, on May 1, to Walter Reed Army Hospital.

On admission there were no abnormal physical findings except for a soft diastolic murmur in the left second interspace and a 2-cm., nontender, freely movable nodule underlying the biopsy

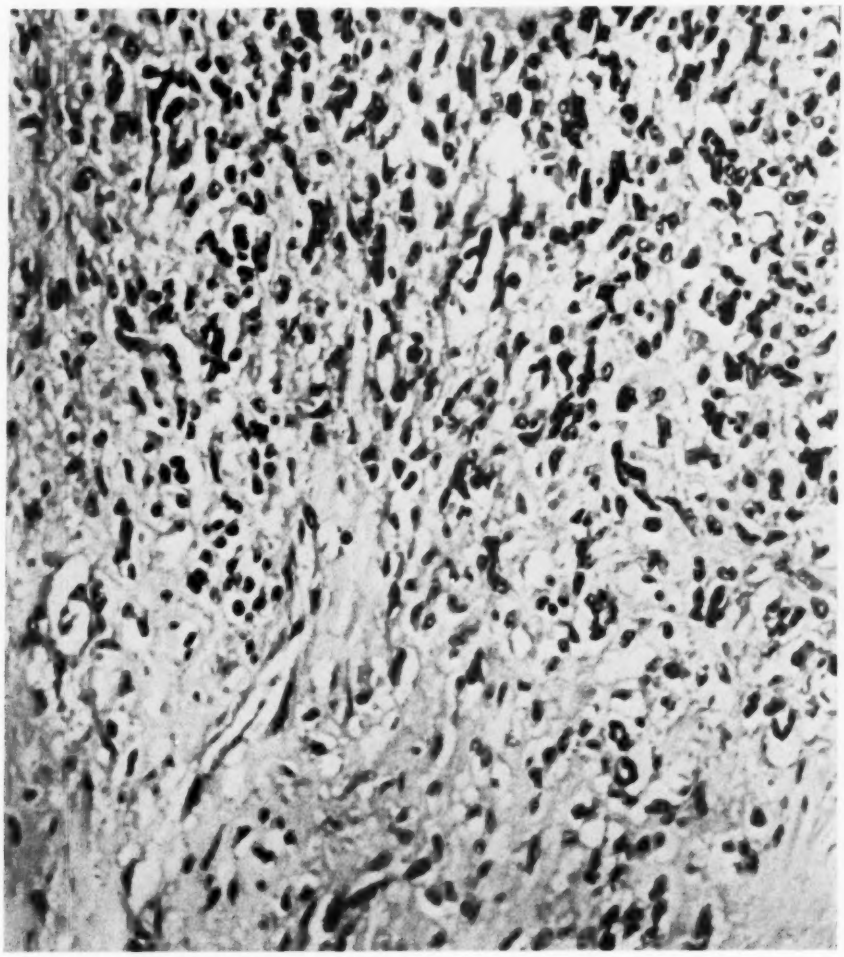


Fig. 7 (Case 2).—Hemangioendothelial sarcoma. Low-power view showing markedly hyperchromatic, pleomorphic spindle-shaped neoplastic cells lining vascular spaces. At periphery, many tumor cells are embedded in dense collagen. × 100.

site. The site of the primary lesion was not found. During his 22 weeks of hospitalization, no anemia developed despite the severity of his illness. Terminally, there were a moderate leucocytosis and mild albuminuria. The patient was given a total of 12,800 r to his left axilla during the next three months of hospitalization. Despite this intensive therapy, the node regressed only slightly in size. A chest roentgenogram on Aug. 13 demonstrated a mottled area of

increased density in the upper field of the left lung. Although no evidence of discrete lesions was seen, it was felt that the mottling was suggestive of metastases. By late August there were numerous subcutaneous metastatic nodules over the lower portion of the left chest. A contemporary complaint was severe painful swelling of the left upper extremity, which rapidly progressed to elephantiasis of the limb. Severe pain developed in the lumbar area; roentgenograms

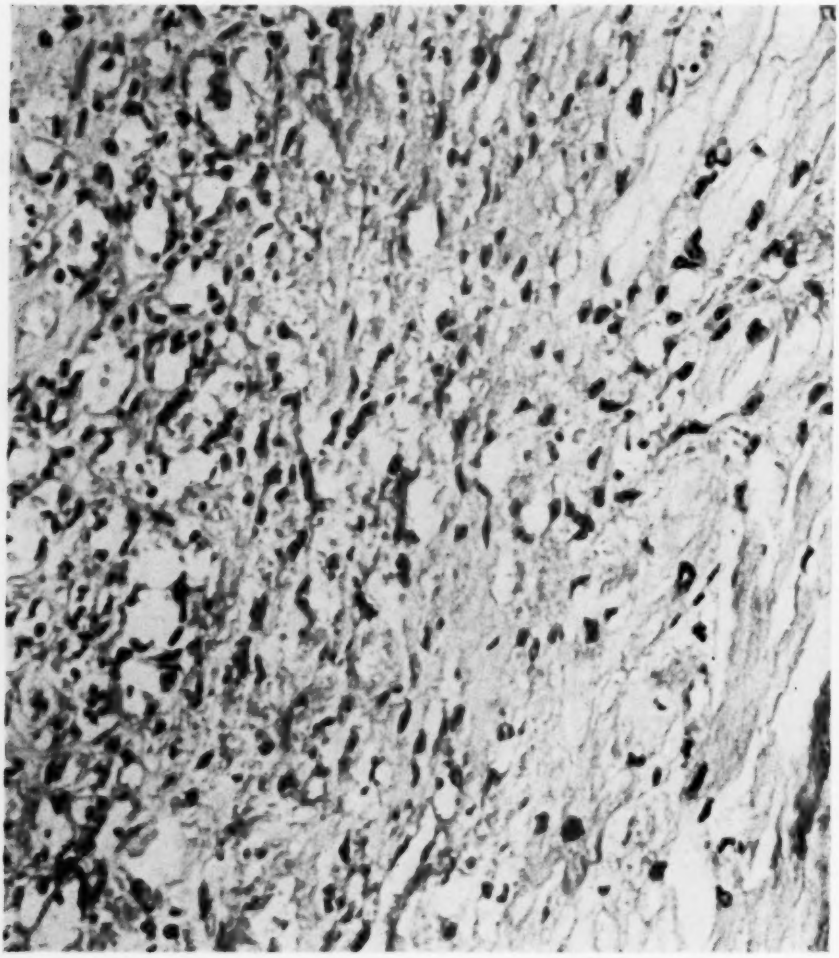


Fig. 8 (Case 2).—Hemangioendothelial sarcoma. Low-power view showing complete replacement of epicardium and invasion of myocardium by tumor. Note marked tendency to sclerosis. This was a prominent feature in all the sections and led to an erroneous diagnosis of sclerosing hemangioma on tissue taken from the right fifth rib lesion during life. × 100.

of the spine revealed no evidence of metastases. By September he noted difficulty in moving his lower extremities; this was soon followed by complete paraplegia. A massive pleural effusion developed, and he continued to fail rapidly. He died on Oct. 16.

Pertinent Necropsy Observations.—The left pectoral area was infiltrated by tumor from the epidermis down to the fascial covering of the thoracic cage. Both parietal pleurae were studded

with grayish-white neoplastic growths, the largest of which measured 3 cm. Each pleural space contained 500 cc. of straw-colored fluid. The mediastinal pleura and parietal pericardium were also studded with grayish-white nodules. The epicardium was smooth and glistening; the pericardial sac contained 40 cc. of straw-colored fluid. The heart weighed 300 gm. The epicardial surface was smooth and glistening. In the interatrial septum there was a 1-cm. tumor nodule in the usual position of the foramen ovale. (From the section available it is obvious that the nodule projected into the lumen of one of the atria, but the protocol does not indicate which one.) The endocardium, valves, and coronary ostia were normal. Mild atheromatous changes were noted in the coronary vessels. The myocardium was soft and flabby; no other gross metastases to the heart were noted. Vast parenchymatous infiltration by grayish-white tumor tissue was

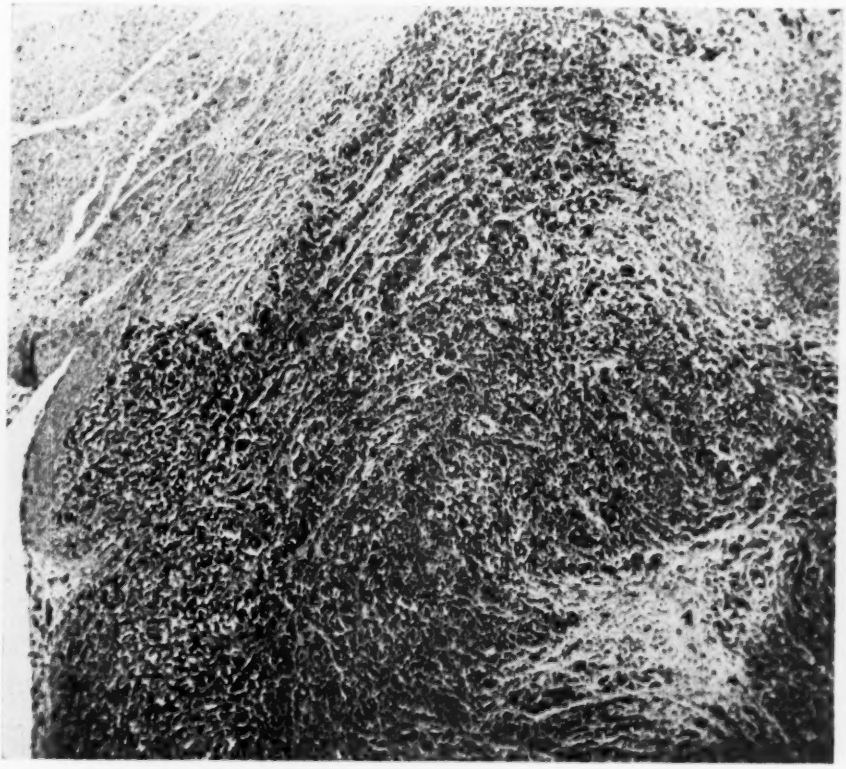


Fig. 9 (Case 3).—Malignant melanoma. Low-power view of tumor nodule in interatrial septum. Note destruction of myocardial fibers at periphery of tumor. × 25.

noted in the liver, which weighed 1,140 gm. Only a few discrete nodules of tumor were present, the malignant process invading in broad, confluent sheets. A small metastatic nodule was observed in the spleen and one in the hilus of the left kidney. The lymph nodes of the mesentery were enlarged and confluent, forming a mass measuring 15 by 10 by 7 cm.

Microscopically, the tumor nodule in the interatrial septum (Fig. 9) was attached to one surface of the septum, invading and destroying portions of the subjacent myocardium. The tumor consisted of sheets and nests of melanoma cells with eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli. No melanin was seen in the section from the cardiac metastasis. Rare pigmented tumor cells from other sites were noted, however, and dopa stains were positive.

Comment.—The single electrocardiogram recorded shortly after admission was normal. No explanation was found for the soft diastolic murmur detected on admission, and there was no change in the murmur during the 22 weeks of hospitalization. There were no cardiac signs or symptoms to arouse suspicion of metastatic involvement of the heart.

CASE 4.—*Squamous-cell carcinoma, left main-stem bronchus, with metastases to lungs, pleura, thoracic wall, diaphragm, mediastinum, pericardium, myocardium, aorta, and bone.*

A white man aged 69 visited the outpatient service of Walter Reed Army Hospital on April 7, 1948, complaining of pain in the left side of his chest and mild hemoptysis of approximately one week's duration. Three months previously he had noted onset of a persistent, nonproductive cough not accompanied by pain or other symptoms. Review of his past and family history was noncontributory. His significant habit consisted of having smoked eight cigars daily for many years until onset of the present illness. Physical examination elicited relative dullness of his left lung base.

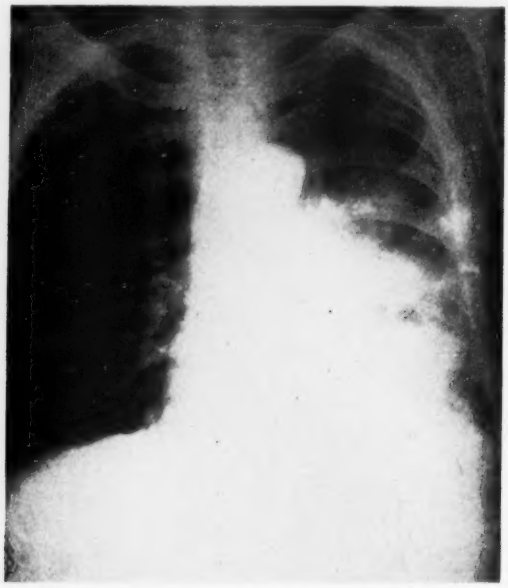


Fig. 10 (Case 4).—Squamous-cell carcinoma of bronchus. Roentgenogram of chest showing left pleural effusion and partial atelectasis of left lower lobe.

A roentgenogram of the chest revealed a small amount of fluid in the left pleural cavity. No neoplastic cells were found in a small quantity of fluid aspirated, but the patient was admitted for observation. A second roentgenogram, on April 26, demonstrated recurrence of left pleural effusion and partial atelectasis of the lower lobe of the left lung, suggesting a neoplasm of the left lung (Fig. 10). Bronchoscopic examination revealed a tumor mass in the left main-stem bronchus, and biopsy of this mass showed undifferentiated squamous-cell carcinoma. Fluoroscopy demonstrated fixation of the left leaf of the diaphragm, and the tumor was regarded as inoperable. High-voltage roentgen irradiation of the tumor area did not favorably influence the slow downhill course of the patient. Fluid obtained by repeated thoracenteses consistently failed to contain neoplastic cells. By January, 1949, he was raising approximately 6 oz. of blood-tinged sputum daily. A roentgenogram of the chest revealed an appreciable enlargement of the mediastinum, with displacement of the trachea leftward and increased left hilar shading. Roentgen survey of the skeleton disclosed no metastases. An electrocardiogram revealed low voltage in all leads.

Despite the probability that these changes reflected the patient's age, it was suspected that they could also be produced by pericardial invasion by tumor. In view of the persistent absence of cancer cells in pleural aspirates, a thoracotomy was done. At surgery, the tumor was found to be not resectable because of diffuse metastases to mediastinal structures. No metastases were observed on the visible pericardium. By March the patient was slightly cachectic; there was no clinical evidence of any heart disorder. Physical examination revealed slight cachexia, normal

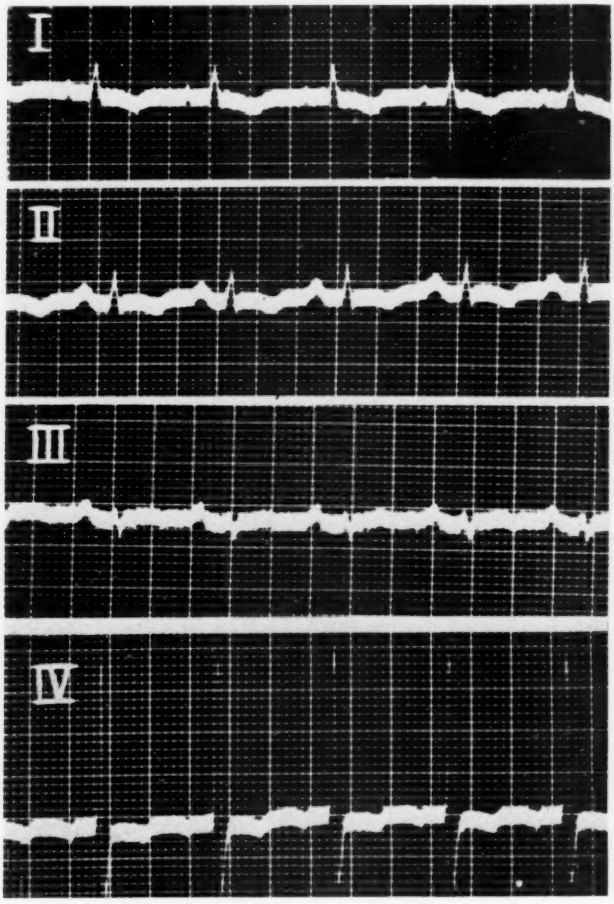


Fig. 11 (Case 4).—Squamous-cell carcinoma of bronchus. Electrocardiogram showing low-voltage in Leads I, II, and III, and inversion of T-I, T-II, and T-IV.

blood pressure, no abnormal heart findings, a shift of the trachea to the left, shotty cervical adenopathy, dullness and splinting of the entire left side of the chest, and scattered rales over both lung fields. The liver edge was barely palpable just below the costal margin. Laboratory examinations showed mild leucocytosis with a preponderance of polymorphonuclear cells. The erythrocyte count, hemoglobin content, and hematocrit reading were normal. The serum protein content was 5.6 gm., albumin-globulin ratio 1.2:1, and sedimentation rate 23 mm. an hour. Urinalysis gave normal results. A roentgenogram of the chest demonstrated considerable shift

of the heart and mediastinum to the left, elevation of the left leaf of the diaphragm, marked infiltration of the left lung except its apical portion, but no evidence of infiltration of the right lung. An electrocardiogram showed decreased voltage of all complexes and elevation of RS-T segments. These abnormalities were interpreted as being suggestive of pericardial involvement by neoplasm.

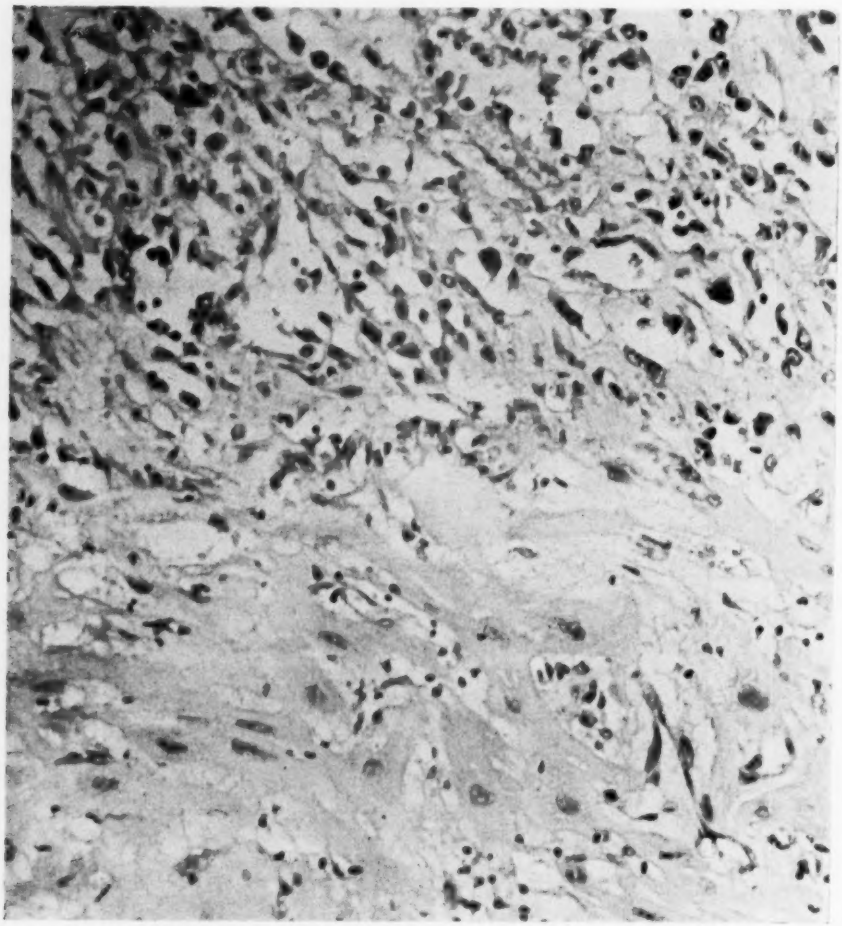


Fig. 12 (Case 4).—Squamous-cell carcinoma of bronchus. Low-power view of heart showing replacement of epicardium and a thin zone of subjacent myocardium by anaplastic squamous-cell carcinoma. × 100.

During March and April the patient's course remained relatively stable; his cough produced copious sputum. Early in May dysarthria developed slowly. An electrocardiogram showed inversion of T waves with low voltage in Leads I, II, and III (Fig. 11). Cheyne-Stokes respiration developed on June 1, and the patient died the following day.

Pertinent Necropsy Observations.—The right lung was grayish-pink, with normal superficial markings. Approximately 300 cc. of yellow fluid was found in the right pleural cavity; the left cavity was obliterated by tumor and fibrous tissue. The pericardium was obliterated and covered

by fat; the pericardial sac was bound by dense fibrous adhesions to the surface of the epicardium, necessitating forceful blunt dissection to separate the structures. The mediastinal lymph nodes were enlarged, replaced by tumor, and bound firmly to tumor extending from the region of the hilum of the left lung. Acute suppurative pneumonia was noted in the left upper lobe. The left lower lobe was widely involved by a necrotic mass of fibrous and neoplastic tissue. The tumor extended directly to the diaphragm and pericardium. The mediastinum was filled with tumor

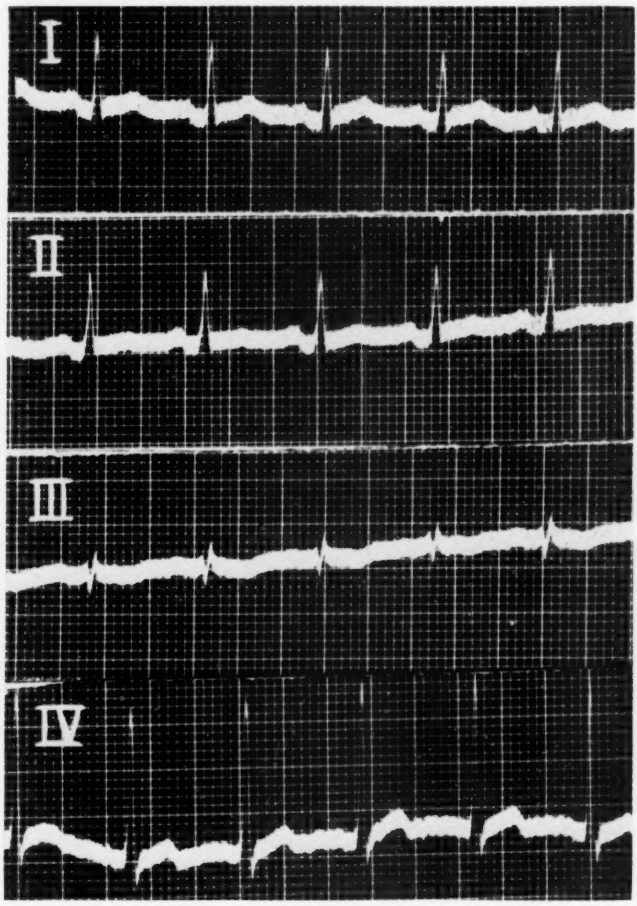


Fig. 13 (Case 5).—Acute lymphogenous leukemia. Electrocardiogram showing low voltage of T waves in Leads II and III, with inversion of T-III and diphasic T-IV.

nodules. The heart was estimated to weigh about 300 gm.; it was impossible successfully to separate the epicardium from the pericardium, because of its fibrous, neoplastic involvement. On opening of the heart, no invasion of the myocardium was seen, the malignant process apparently being limited to the superficial portion of the epicardium. The myocardium and endocardium appeared normal. The average thicknesses of the right and left ventricular walls were 0.4 and 1.3 cm., respectively. The coronary arteries were slightly sclerotic but patent throughout. All the great vessels in the mediastinum, including the aorta, were studded externally with tumor nodules.

Microscopically, the tumor was an anaplastic squamous-cell carcinoma arising in the left main-stem bronchus. There was extensive invasion of the epicardium and myocardium superficially, with tumor cells destroying the muscle fibers (Fig. 12).

Comment.—Despite the extensive involvement of the pericardium and the lesser, but significant, involvement of the superficial myocardium by metastatic tumor, there was no clear-cut clinical evidence of cardiac invasion. Two abnormal electrocardiograms were regarded as possibly reflecting pericardial invasion by tumor.

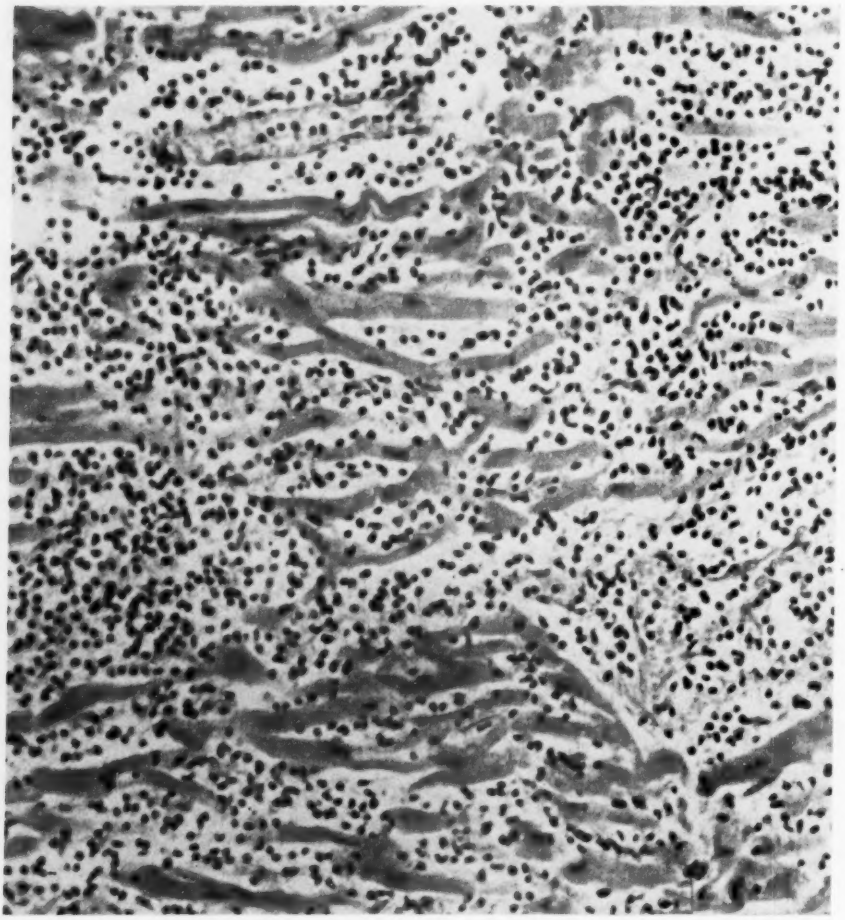


Fig. 14 (Case 5).—Acute lymphogenous leukemia. Low-power view of myocardium. Observe separation, fragmentation, and atrophy of myocardial fibers and leukemia cells infiltrating stroma between muscle fibers. × 100.

CASE 5.—*Acute lymphogenous leukemia with infiltration and obliteration of the pericardial sac, and widespread infiltration of the myocardium and other organs and structures.*

A white man aged 33 was in good health until November, 1943, at which time he noted easy fatigability and lassitude. During the next three months these symptoms increased. Exertional dyspnea developed three weeks prior to admission to Walter Reed Army Hospital on March 16,

1944. Questioning revealed a recent history of night sweats and bleeding gums following brushing of teeth. A review of his past history, family history, and habits was noncontributory.

Physical examination revealed slight limitation of expansion of the right lung, with relative dullness over the right base and occasional rales. The heart sounds were distant, but otherwise no cardiac abnormalities were heard. However, on percussion the heart was found to be moderately enlarged both to the right and to the left. The neck veins were distended, and the liver was slightly enlarged. Generalized adenopathy was present. A white blood cell count revealed over 50,000 leucocytes per cubic millimeter; 90% of the cells were immature lymphoid cells. A diagnosis of acute lymphogenous leukemia was made. A roentgenogram of the chest showed a moderate generalized enlargement of the cardiac shadow. A pericardial paracentesis netted only 5 cc. of serosanguinous fluid. An electrocardiogram showed a simple sinus tachycardia, rate 114, a low voltage of T waves in Lead II and inversion of T-III, and diphasic T-IV (Fig. 13). Supportive therapy was of no avail; the heart sounds became progressively more distant, and the patient died on May 1.

Pertinent Necropsy Observations.—Both lungs were partially obliterated by dense fibrous adhesions. The right and left pleural cavities contained 200 and 300 cc. of blood-tinged fluid, respectively. The anterior wall of the pericardium was firmly adherent to the sternum. The wall of the pericardium averaged 2 cm. in thickness; no pericardial cavity remained. There was complete envelopment of the heart by pale, fleshy tumor which constricted both the heart and the great vessels at its base. The myocardium was pale; the valves, coronary arteries, and their ostia were not remarkable. The liver weighed 1,799 gm.; no gross tumor was observed. Dense infiltration of the pancreas, spleen, kidneys, and intestines was noted.

Microscopically, the lymph nodes showed complete destruction of the normal architecture and replacement by sheets of immature lymphoid cells. Sections of the heart showed obliteration of the pericardial sac and replacement of the epicardium and pericardium by a thick layer consisting of sheets of immature lymphoid cells. In one section these cells extended deep down into the myocardium, producing separation and destruction of muscle bundles (Fig. 14).

Comment.—This patient presented the signs of distended neck veins, generalized cardiac enlargement to percussion, distant heart sounds, hepatomegaly, roentgenographic evidence of cardiac enlargement, and abnormal electrocardiograms. The occurrence of these findings in a young person with known leukemia, with no heart murmurs and no previous known heart disease or symptoms thereof, strongly suggested, clinically, leukemic involvement of the heart. There was no record of cytological examination of the pericardial aspirate obtained shortly after admission.

Col. Thomas W. Mattingly, Medical Corps, United States Army, Chief, Cardiovascular-Renal Section; Miss Rose L. Clarke, Department of Pathology, and Miss Bonita Goodwin, Secretary, Tumor Registry, Pathology Department, Walter Reed Army Hospital, assisted in the preparation of this paper.

CARDIOVASCULAR LESIONS FOLLOWING BILATERAL NEPHRECTOMY OF DOG

Role of Hypertension and Other Factors on Pathogenesis

E. E. MUIRHEAD, M.D.
J. A. STIRMAN, M.D.
FRANCES JONES, M.S.
WARREN LESCH, M.A.
MARJORIE BURNS, B.S.
AND
M. J. FOGELMAN, M.D.
DALLAS, TEXAS

A FUNDAMENTAL role of the kidney in the maintenance of the integrity of the heart and arteries is suggested by the development of severe cardiovascular lesions following bilateral nephrectomy and other experimental manipulations of the kidney associated with renal insufficiency.[1] The development of prominent hypertension after some of these renal manipulations, plus the occurrence of vascular lesions similar to certain vascular lesions of the human in malignant hypertension, has led to the concept that the hypertension per se causes the

This study was supported by a grant from the United States Public Health Service.

From the Department of Pathology of the Southwestern Medical School of the University of Texas.

1. (*a*) Muirhead, E. E.; Vanatta, J., and Grollman, A.: Hypertensive Cardiovascular Disease: An Experimental Study of Tissue Changes in Bilaterally Nephrectomized Dogs, Arch. Path. **48**:234, 1949; (*b*) Hypertensive Cardiovascular Disease ("Malignant Hypertension"): Changes in Canine Tissue Induced by Various Manipulations of the Kidney, with Special Reference to Vascular and Myocardial Lesions, ibid. **50**:137, 1950. (*c*) Muirhead, E. E.; Turner, L. B., and Grollman, A.: Hypertensive Cardiovascular Disease: Vascular Lesions of Dogs Maintained for Extended Periods Following Bilateral Nephrectomy and Ureteral Ligation, A. M. A. Arch. Path. **51**:575, 1951; (*d*) Hypertensive Cardiovascular Disease: Nature and Pathogenesis of the Arteriolar Sclerosis Induced by Bilateral Nephrectomy as Revealed by a Study of Its Tinctorial Characteristics, ibid. **52**:266, 1951. (*e*) Goldblatt, H.: Anatomical Considerations of Hypertension, in Hypertension, edited by E. T. Bell, Minneapolis, University of Minnesota Press, 1951, p. 5. (*f*) Winternitz, M. C.; Mylon, E.; Waters, L. L., and Katzenstein, R.: Studies on the Relation of the Kidney to Cardiovascular Disease, Yale J. Biol. & Med. **12**:623, 1940. (*g*) Winternitz, M. C., and Waters, L. L.: Lesions of the Larger Vessels Following Renal Artery Constriction, ibid. **12**:451, 1940. (*h*) Holman, R. L.: Studies on the Pathogenesis of Arterial Lesions, in Year Book of Pathology and Clinical Pathology, 1951, edited by H. T. Karsner, and A. H. Sanford, Chicago, Year Book Publishers, Inc., 1951, p. 101. (*i*) Wilson, C., and Pickering, G. W.: Acute Arterial Lesions in Rats with Experimental Renal Hypertension, Clin. Sc. **3**:343, 1938. (*j*) Wilson, C., and Byrom, F. B.: Renal Changes in Malignant Hypertension: Experimental Evidence, Lancet **1**:136, 1939. (*k*) Byrom, F. B., and Dodson, L. F.: The Mechanism of the Vicious Circle in Chronic Hypertension, Clin. Sc. **8**:1, 1949.

vascular lesions.[2] Some workers,[3] however, have considered that disturbances associated with renal failure induce the lesions. Another school of thought implicates dietary influences in the genesis of the vascular lesions.[1h] Thus the pathogenesis of these important cardiovascular lesions remains obscure. Yet, it is likely that an understanding of the pathogenesis of these experimental cardiovascular lesions not only would add to the understanding of malignant hypertension but might also serve to elucidate certain aspects of uremia itself.

The extension of the life of the dog after bilateral nephrectomy and other renal disturbances by means of dialyzing procedures yields an experimental preparation with a high incidence of cardiovascular lesions and affords an opportunity for observation of the role of various factors on the genesis of the cardiovascular injury.

In the present article it is proposed to discuss additional experience with the muscular changes of the heart and systemic arteries following bilateral nephrectomy and to analyze the role in their genesis of a series of factors associated with the extension of life by peritoneal irrigation. In addition, the incidence of cardiovascular lesions in the experiments herein reported is compared with the incidence in previously reported groups.

METHODS

Fifty-six adult mongrel dogs of both sexes weighing 6 to 18 kg. were used. Through the posterior approach, removal of one kidney was performed, followed about one week later by removal of the second kidney. The first kidney was removed with the animal under sodium pentobarbital anesthesia, while the second kidney was removed during ether anesthesia. The preuremia studies (of arterial pressure, body weight, blood urea, blood volume) were performed between the two operations. Immediately after the second nephrectomy, peritoneal irrigation was started. During the daytime 1 to 2 liters of fluid was introduced into the peritoneal cavity, allowed to remain three to four hours, and then drained off without suction by means of a 16-gauge needle and a rubber tube. Overnight the fluid remained in the peritoneal cavity for approximately 14 hours. In most experiments fluid with the following composition per liter was used: NaCL 5.77 gm., $NaHCO_3$ 3.45 gm., KCl 0.2 gm., $CaCl_2$ 0.2 gm., $MgCl_2$ 0.9 gm., dextrose 10 to 30 gm., and oxytetracycline (terramycin®) [4] 100 mg., which produced the following ionic composition per liter; Na 141 mEq., K 2.7 mEq., Ca 3.6 mEq., Mg 1.5 mEq., Cl 108 mEq., and HCO_3 41 mEq. The diet consisted of a homogenized formula, 100 cc. of which contained peanut or cocoanut oil 40 cc., dextrose 30 gm., protein 14 gm., water to volume, and the following supplements: thiamine hydrochloride 1 mg., riboflavin 1 mg., pyridoxine hydrochloride 0.4 mg., yeast extract 3 gm., liver concentrate 0.4 gm., calcium pentothenate 2 mg., nicotinamide 6 mg., folic acid 0.4 mg., cod liver oil 8 drops, tocopherol 8 drops, ascorbic acid 200 mg., choline chloride 40 mg., and vitamin K (menadione) 1 mg. Of this formula, 150 to 200 cc. was given by mouth daily.

The animals were weighed daily. The mean arterial pressure, which was recorded each morning, was obtained by means of direct femoral artery puncture and a mercury manometer. The urea determinations were performed by the method of Blair and Taylor.[5] The blood volume was estimated by the T-1824 dye procedure of Mayerson and co-workers.[6] Wintrobe's method [7]

2. Wilson and Pickering.[1i] Wilson and Byrom.[1j] Byrom and Dodson.[1k]

3. Goldblatt.[1e] Winternitz and others.[1f] Winternitz and Waters.[1g]

4. Furnished by Chas. Pfizer & Company, Inc.

5. Taylor, W. F., and Blair, W. M.: Improved Method for Determination of Blood Urea Nitrogen by Direct Nesslerization, J. Lab. & Clin. Med. **17**:1256, 1932.

6. Mayerson, H. S.; Lyons, C.; Parson, W.; Nieset, R. T., and Trautman, W. V.: Comparisons of Results of Measurement of Red Blood Cell Volume by Direct and Indirect Technics, Am. J. Physiol. **155**:232, 1948.

7. Wintrobe, M. M.: A Simple and Accurate Hematocrit, J. Lab. & Clin. Med. **15**:287, 1929.

was used for the hematocrit reading. After death all animals were examined, and sections of tissue from various organs were prepared in the usual manner after fixation in 10% formalin and Zenker's fluid.

Homogenous renal transplants were used in one group of animals. The donor kidney in the homogenous renal transplantation was transferred to the neck of the recipient, the renal artery and vein being anastomosed to the carotid artery and jugular vein, respectively. The ends of the donor's renal vessels were immersed in 10% formalin for one minute before the anastomosis in order to minimize disruption. The anastomosis was performed with the animals under ether anesthesia and required about 45 minutes. The ureter was brought out through the skin. Other details of this procedure and its results form the basis of another report.

RESULTS

The 56 dogs of the present series survived from 6 to 38 days after the removal of the second kidney. The animals have been divided into three survival groups. In the first two groups life was extended by means of peritoneal irrigation alone, while in the third group peritoneal irrigation was supplemented by the addition of a functioning homogenous renal transplant on the 8th to 14th day. The first

TABLE 1.—*Types of Myocardial Lesions*

Survival Group	No. of Dogs	No. with Lesions	Acute Lesions			Healed Lesions				
			Microscopic Necrosis	Necrosis and Calcification	Gross Necrosis	Microscopic Early Scar	Large Early Scar	Hyaline Scar	Hemorrhages	Arterial Lesions
I. 6-9 days	15	9	3	1	3	2	0	0	4	4
II. 10-24 days	28	13	7	2	5	3	2	0	4	6
III. 15-38 days; renal transplant	8	6	1	0	1	2	1	3	3	0
Total	51	28	11	3	9	7	3	3	11	10

group survived for 6 to 9 days (15 dogs), the second group survived for 10 to 24 days (33 dogs), and the third group survived for 15 to 38 days (8 dogs).

CARDIOVASCULAR LESIONS, EMPHASIS ON MUSCULAR CHANGES

Myocardial Lesions.—Table 1 lists the various myocardial lesions detected within the three survival groups. The incidence of detectable lesions amounted to 56% for Group I, 46.5% for Group II, and 75% for Group III. Thus, out of a total of 51 dogs, 28, or 55%, yielded detectable gross or microscopic cardiac lesions.

Extension of the survival revealed an expected variation in the appearance of the myocardial lesions. The three major myocardial lesions consisted of necrosis of myocardial fibers, fibrosis, and hemorrhages. The hemorrhages occurred in one-half of the animals showing lesions and were equally distributed in the three groups. Myocardial and subendocardial hemorrhages were observed, the latter being commoner. Both sides of the heart were the seat of hemorrhages, although the most prevalent site was the subendocardial region of the left ventricle over the papillary muscles and about the apex (Fig. 1). In all but one case the hemorrhages were associated with evidence of injury to myocardial fibers. Thus, the hemorrhages appeared to be mainly a complication of myocardial injury.

The injury to myocardial fibers manifested itself in necrosis and fibrous replacement of fibers. Grossly detectable foci of necrosis were encountered in 43% of the animals showing lesions (25% of the total), being slightly commoner in

Group I than in the other groups. Microscopic foci of necrosis involved either a few groups of fibers or single fibers. In each case the fibers revealed a minute focus of disintegration, on each side of which normal myocardium was evident. Transitions were noted between isolated fiber necrosis involving a microscopic segment of a single myocardial fiber (Fig. *2A*), microscopic necrosis involving a tiny bundle of fibers (Fig. *2B*), and larger areas of necrosis at times involving almost an entire papillary muscle or almost the thickness of the left ventricle Fig. *3D*). Most areas of necrosis showed recent hemorrhages and the infiltration of polymorphonuclear neutrophilic leucocytes (Fig. *3A*).

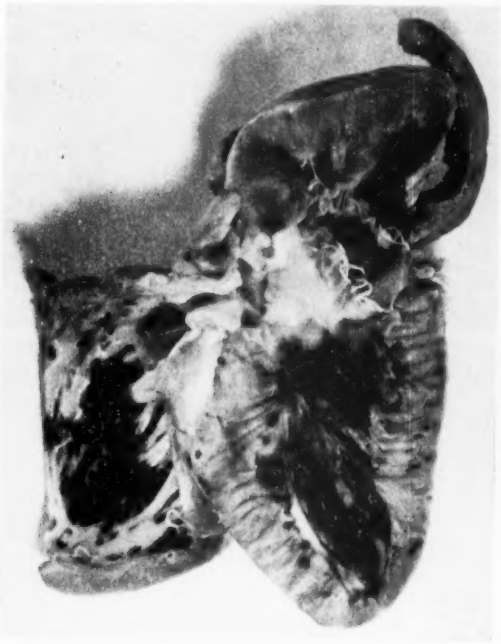


Fig. 1.—Dog 183, which survived eight days; blood pressure was 170 mm. Hg. Gross picture of heart showing widespread subendocardial hemorrhages of both ventricles and areas of hemorrhagic necrosis in wall of left ventricle.

Early scars varied in size, the most prevalent being of microscopic proportions. Gaps in the myocardium were filled with a mixture of plump fibroblasts, a few fibrils, and pigment-laden macrophages (Figs. *2B* and *3C*). These foci eventually changed to fibrous scars (Fig. *3B*). The early scars were uncommon in Group I but became prevalent after 10 days of survival. Fibrous scars were encountered only in Group III. These sequences are the expected changes in the temporal progress of the repair process as it involves the heart.[8]

8. Karsner, H. T., and Dyer, J. E.: Studies in Infarction: Experimental Bland Infarction of the Myocardium, Myocardial Regeneration and Cicatrization, J. M. Res. **34**:21, 1916. Mallory, G. K.; White, P. D., and Salcedo-Salgar, J.: The Speed of Healing of Myocardial Infarction: Study of Pathologic Anatomy in 72 Cases, Am. Heart J. **18**:647, 1939.

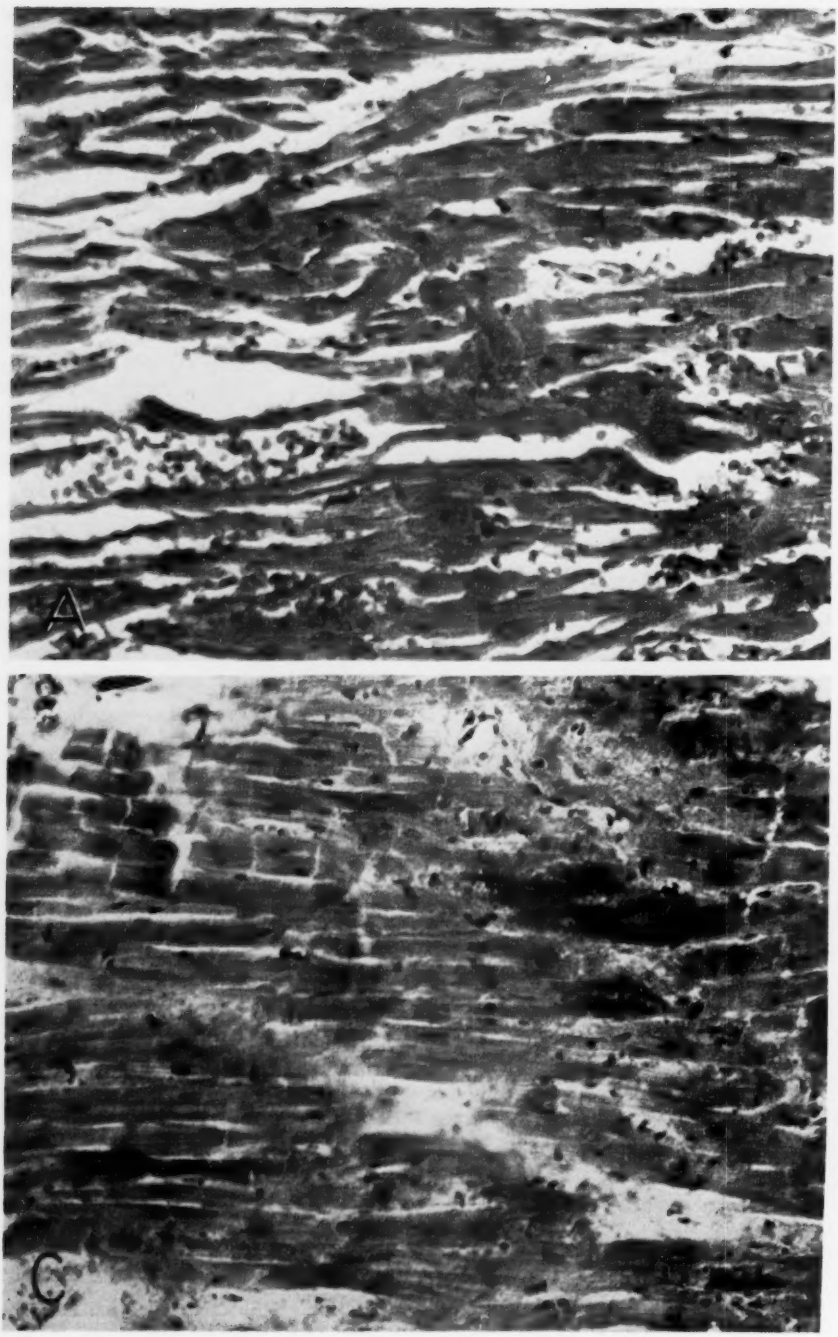


Fig. 2 (Part 1).—*A*, Dog 31, which survived seven days; heart, × 360. Center of photograph demonstrates necrosis of isolated segments of myocardial fibers. The fibers appear spread apart, granular, and partly smeared at involved foci. *C*, Dog 130, which survived 10 days; heart, × 300. Isolated foci of necrosis and calcification of myocardial fibers. Dark areas represent calcium salts.

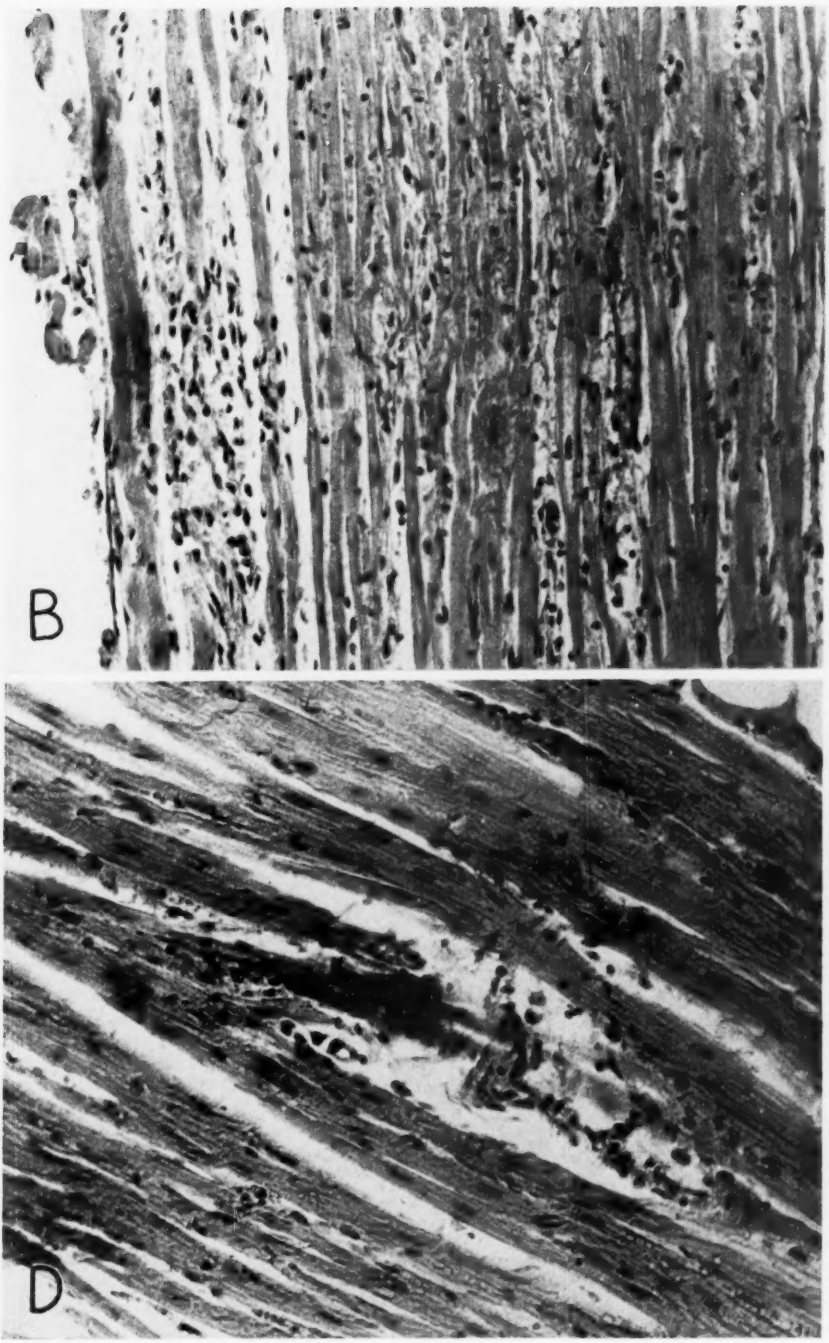


Fig. 2 (Part 2).—*B*, Dog 50, which survived 14 days; heart, × 250. On left, near endocardial surface, there is a young microscopic scar composed mainly of plump fibroblasts. On right there is a microscopic bundle of necrotic myocardial fibers. *D*, Dog 178, which survived six days; heart, × 325. Focal necrosis and calcification of a myocardial fiber.

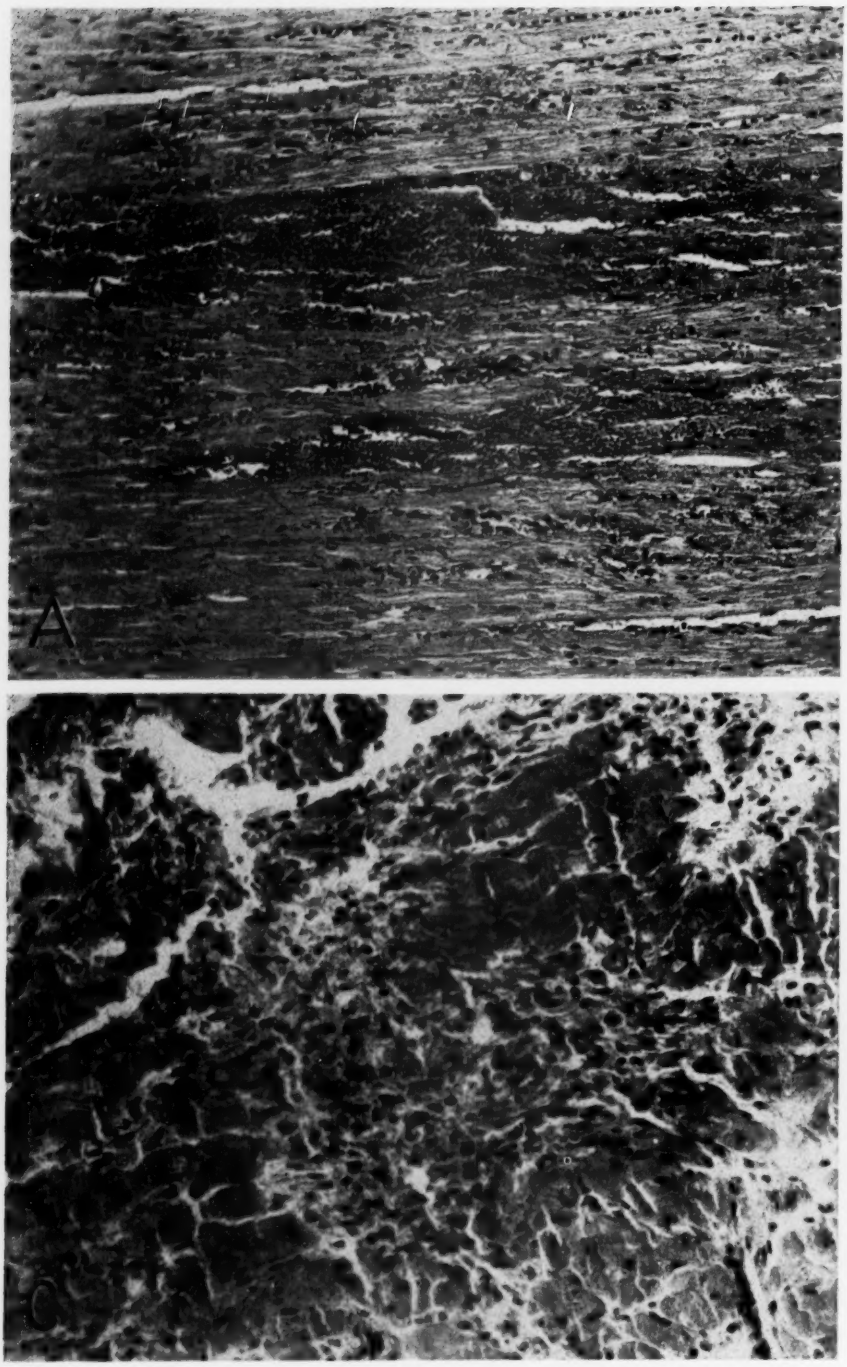


Fig. 3 (Part 1).—*A*, Dog 162, which survived 15 days; heart, × 140. Focal necrosis and hemorrhages of myocardium. *C*, Dog 49, which survived 21 days; heart, × 250. Early microscopic scar bridging a gap in myocardium. There are young fibroblasts, fibrils, and pigment-containing macrophages.

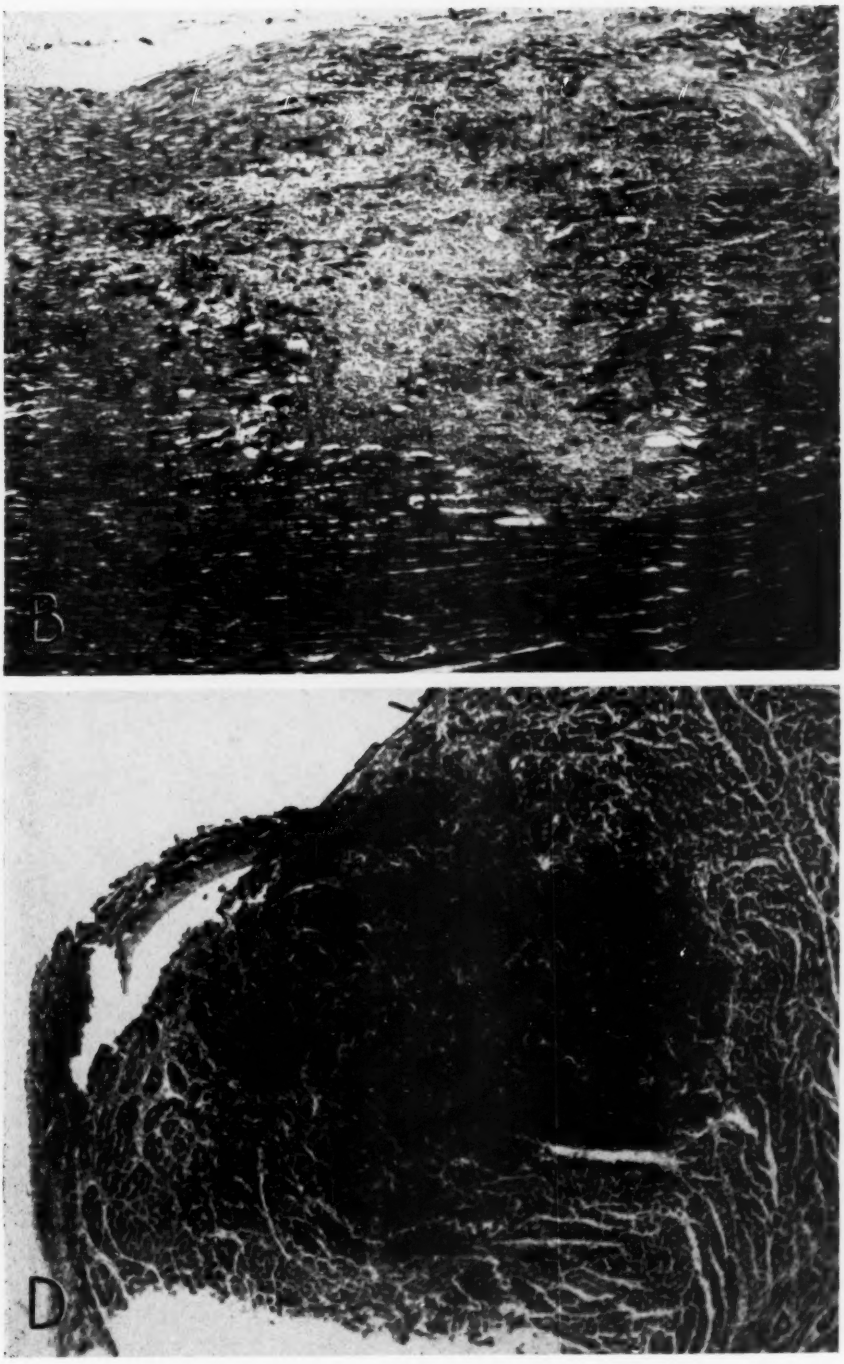


Fig. 3 (Part 2).—*B*, Dog 44, which survived 17 days; heart, × 50. Larger scar replacing a focus of necrosis of left ventricle near endocardium. *D*, Dog 41, which survived 14 days; heart, × 50. Focus of acute necrosis of heart near endocardium.

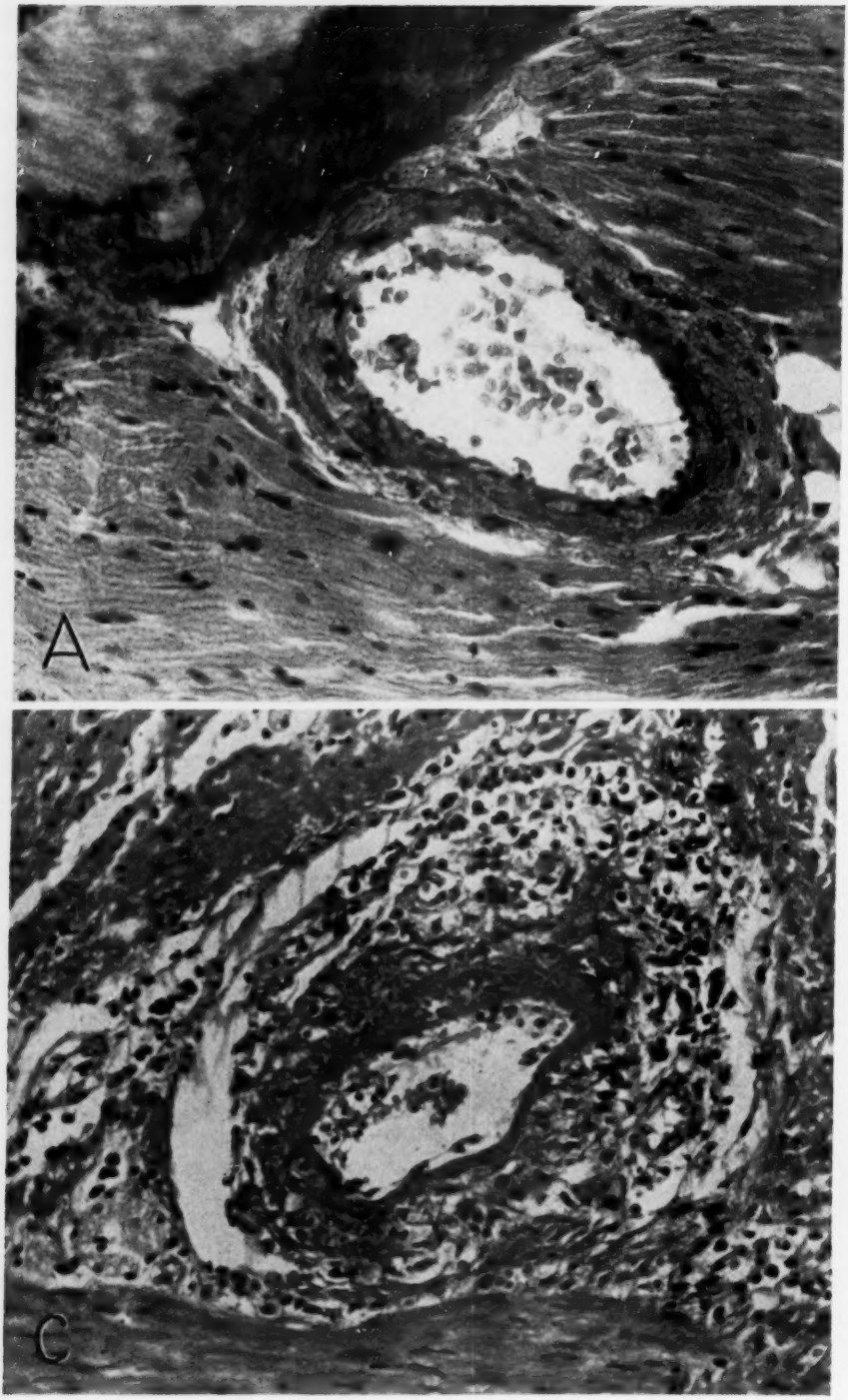


Fig. 4 (Part 1).—*A*, Dog 136, which survived 14 days; heart, × 325. Small artery within myocardium showing necrosis of isolated smooth muscle fibers of media. Individual fibers are swollen and devoid of nuclei. *C*, Dog 40, which survived eight days; stomach, × 350. Small artery in submucosa of stomach showing diffuse necrosis of media, with smearing and smudging toward adventitia. Scattered inflammatory cells, mainly lymphocytes, are present in adventitia.

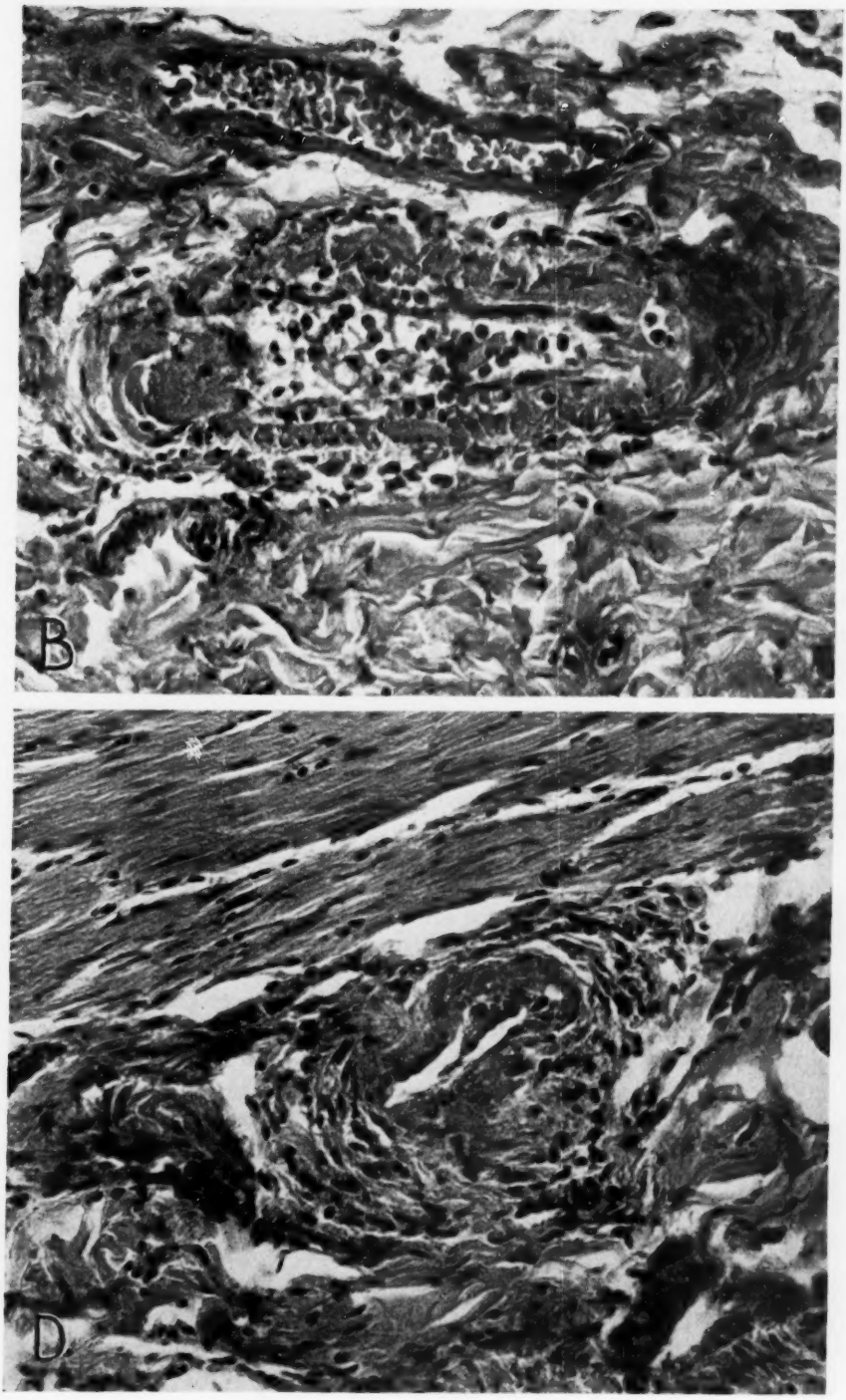


Fig. 4 (Part 2).—*B*, Dog 34, which survived 14 days; bowel, × 400. Small artery in submucosa of bowel. There is necrosis of individual fibers of media, with coalescence and smudging in left and right extremes of this vessel. *D*, Dog 72, which survived 18 days; bowel, × 360. Small artery in submucosa of bowel showing diffuse necrosis and smudging of media and early adventitial fibrosis.

Calcified necrotic myocardial fibers were encountered in three dogs. The calcification at times served to emphasize the isolated characteristics of the necrosis, for microscopic segments of single fibers became bold in relief when not only necrotic but calcified as well (Fig. 2, *C* and *D*).

The nature of the necrosis and repair of the myocardium became additionally emphasized in the present series when these changes were related to the arterial and arteriolar lesions within the myocardium. In the present series, arterial lesions within the myocardium were encountered in 10 of the 51 dogs (19.5%), whereas recent myocardial necrosis was encountered in 23 of the 51 animals (45%); however, among the 10 dogs revealing lesions of small coronary arteries and arterioles, evident myocardial lesions were detected in only three hearts. Thus, of the 28 hearts displaying all types of damage of myocardial fibers, an overwhelming number did not reveal nearby arterial lesions. Although the disparity between myocardial necrosis and fibrosis and arterial lesions has been described in former reports,[9] the dissociation appeared to be more clear-cut in the present series of dogs. These observations are considered to strengthen the concept that the myocardial necrosis results from a direct injury to the cardiac fibers rather than being mediated via vascular lesions. The dissociation between cardiac and vascular injury was particularly apparent in the instances of isolated fiber necrosis, microscopic necrosis of small bundles of fibers, and the microscopic gaps filled with early scars, for these changes usually occurred in the absence of vascular lesions within the myocardium.

Arterial and Arteriolar Lesions.—Table 2 contains the incidence of various types of lesions involving small arteries and arterioles in the three survival groups. The incidence of all types of arterial lesions was similar in the various groups, namely 62% in Group I, 51% in Group II, and 50% in Group III. The over-all incidence of vascular lesions was 55%. As with the myocardial lesions, extension of survival modified the appearance of the vascular changes.

The lesions of arteries and arterioles were encountered in the gastrointestinal tract, heart, and pancreas; about the adrenals, and in the urinary bladder, mesentery, skin, and brain. The commonest site was the submucosa of the stomach and intestines, while the urinary bladder and heart were next in order of frequency. The other sites were involved in isolated cases. The kidneys served as controls and in each case were found to have a normal appearance, including the presence of normal arteries and arterioles.

The injury of small arteries and arterioles was characterized fundamentally by necrosis and degeneration of the smooth muscle of the media. Three variants of necrosis were observed. In the first variant the bulk of the media appeared intact, but isolated smooth muscle fibers or small groups of fibers contained within a segment of the circumference revealed a reddish swelling associated with pyknosis of the nucleus or outright necrosis with an eosinophilic disintegration of the fiber or fibers (Fig. 4 *A* and *B*). This isolated necrosis of the media was observed in eight dogs (14%). Although rare, this lesion identified the primary site of injury and, at the same time, represented a transitional link between the normal intact media and the completely disintegrated and necrotic media. The second form of necrosis consisted of a total disintegration of the smooth muscle of the media

9. Muirhead, Vanatta, and Grollman,[1a,b] Muirhead, Turner, and Grollman.[1c,d]

(Fig. 4, *C* and *D*). The nuclei vanished, and the remaining necrotic sarcoplasm spread out, took a deep eosinophilic stain, and appeared smeared or smudged, giving the appearante of so-called fibrinoid necrosis. On rare occasions the necrotic media, as formerly described, spilled into the lumen and blocked it, a form of thrombonecrosis of the vessel. In most instances, however, the endothelium remained remarkably intact and the lumen was filled with unclotted blood, indicating the ability of these altered vessels to serve as conduits for blood. Such necrotic media usually spread out toward the adventitia. The third type of necrosis entailed a change in the appearance of the necrotic smooth muscle. The necrotic muscle, although still deeply eosinophilic, assumed a hardened and denser appearance, within which remnants of nuclei, in the form of pyknosis and karyorrhexis, could be seen (Fig. 5*A*). This change made the media assume the appearance of the early phases of hyalinization (Fig. 5, *B*, *C*, and *D*). There appeared to be transitions between isolated fiber necrosis, confluent necrosis of the media, and necrosis with a hardening that suggested the early phases of hyalinization. Additional vascular lesions in this series entailed changes toward hyalinization of the vessel wall (Fig. 6, *B* and *C*), and the presence of connective tissue elements within the blood vessel (Fig. 6, *A* and *D*).

TABLE 2.—*Types of Arterial (Arteriolar) Lesions*

Survival Group	No. of Dogs	No. with Lesions	Focal Necrosis, Media	Acute Diffuse Necrosis, Media	Necrosis with Early Hyalinization	Hyalinization	Fibrosis	Calcified Necrotic Media
I. 6-9 days	15	10	4	6	5	1	2	0
II. 10-24 days	33	17	3	10	7	2	2	1
III. 15-38 days; renal transplant	8	4	1	1	1	3	1	0
Total	56	31	8	17	13	6	5	1

A progression of the various arterial lesions appears evident from a piecing together of the various types in a transitional manner. Thus, there was isolated medial necrosis, complete medial necrosis with smudging, medial necrosis with hardening, or early hyalinization and ultimately hyalinization with or without fibrosis. The pathogenesis of the vascular lesions seemed to be associated with changes in the properties of the necrotic smooth muscle leading to hyalinization. Thus, the various forms of vascular lesions appeared to be, not a consequence of different pathogenetic mechanisms, but rather a morphological evolution originating from the injured media.

As on former occasions, necrosis and early hyalin were particularly evident in Group I and Group II. Hyalinization appeared in Group II, becoming particularly evident in Group III. Extension of survival favored the development of the sclerotic changes.

RELATIONSHIP OF VARIOUS FACTORS TO THE CARDIOVASCULAR LESIONS

1. *Relationship of Hypertension to Cardiovascular Lesions.*—Table 3 contains the data dealing with the relationship of arterial hypertension to the frequency of cardiovascular lesions. The evaluation of hypertension was elicited by the daily determination of the mean arterial pressure as obtained by direct femoral-artery

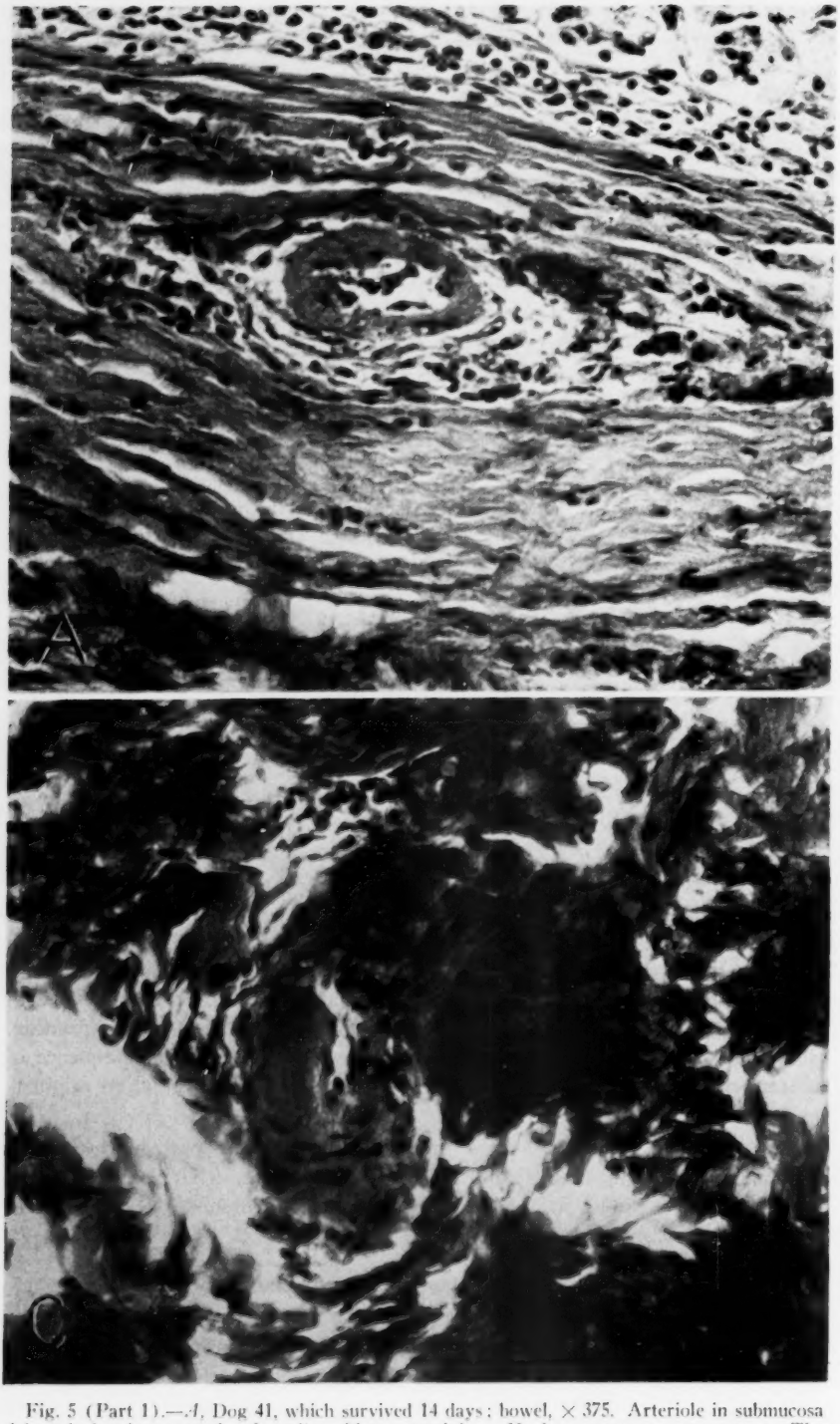


Fig. 5 (Part 1).—*A*, Dog 41, which survived 14 days; bowel, × 375. Arteriole in submucosa of bowel showing necrosis of media without smudging. Nuclear remnants are present. The necrotic media has fused and is assuming a "hardened" appearance. *C*, Dog 133, which survived 14 days; bowel, × 360. Small artery of submucosa of bowel showing focal necrosis of media, with changes toward hyalinization.

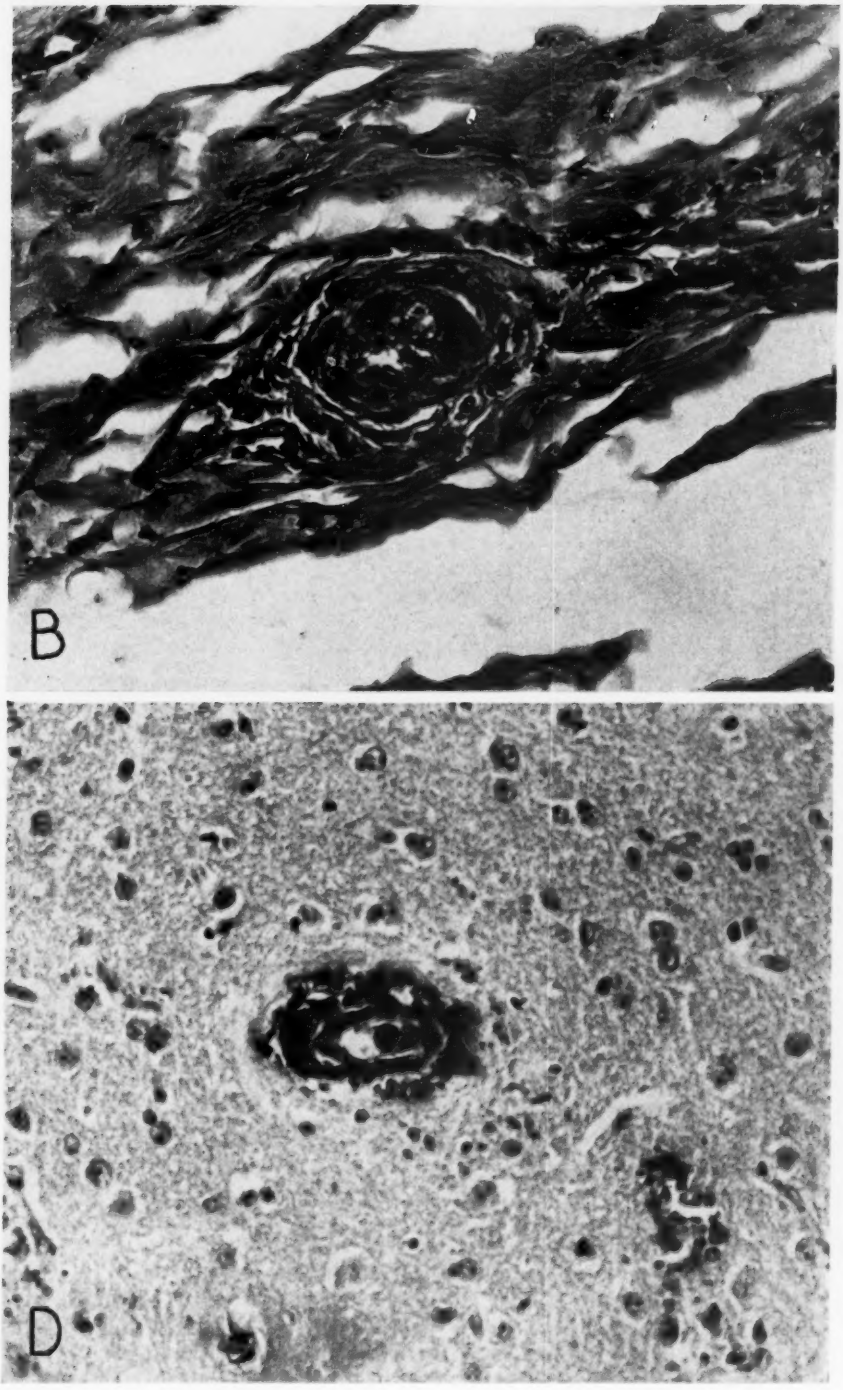


Fig. 5 (Part 2).—*B*, Dog 47, which survived seven days; bowel, × 360. Arteriole of submucosa of bowel showing necrosis and early hyalinization of media causing thickening of wall. *D*, Dog 44, which survived 17 days; brain, × 400. Arteriole in brain showing necrosis of media, with fusion of necrotic remnants resembling hyalinization. Some of the necrotic media has spilled into lumen.

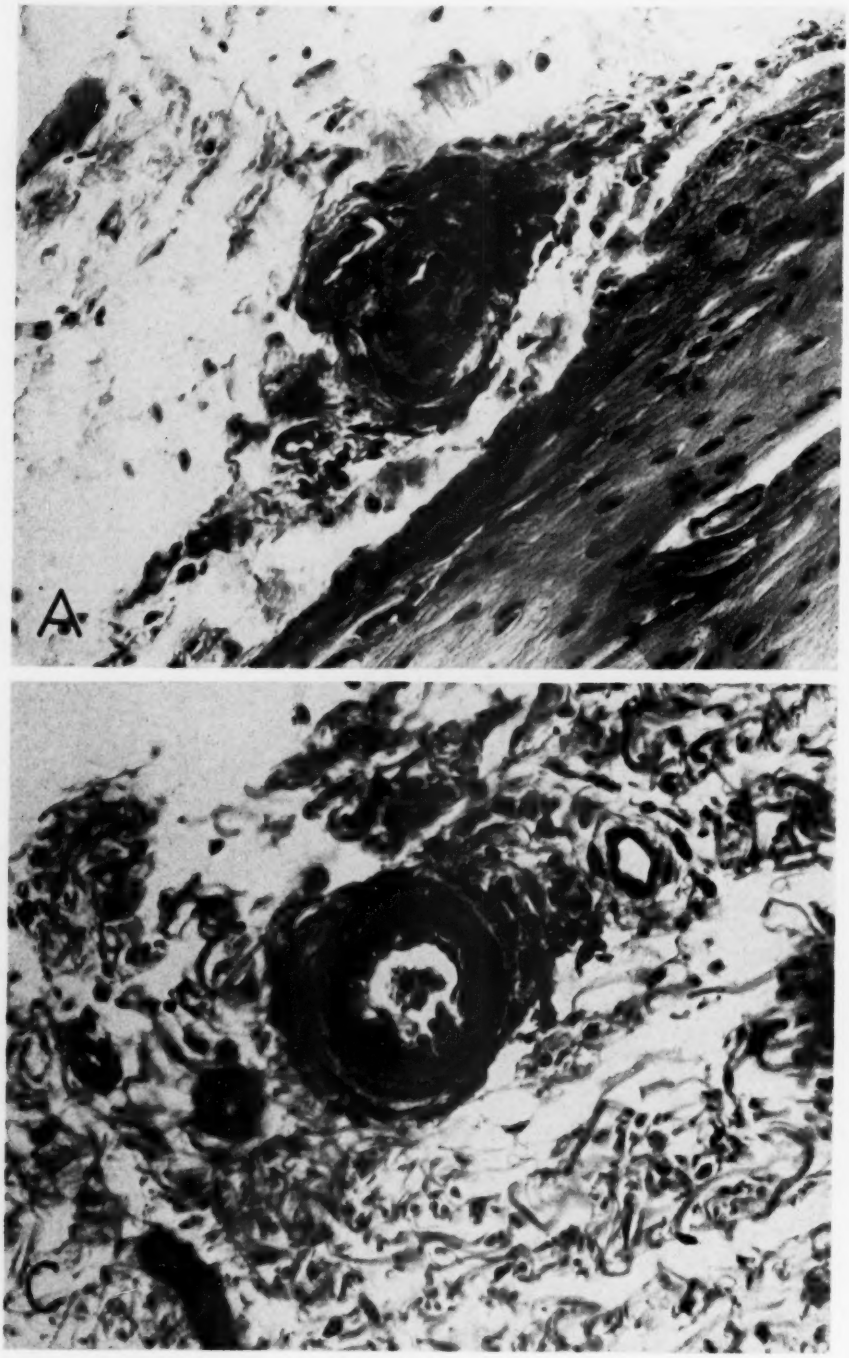


Fig. 6 (Part 1).—*A*, Dog 47, which survived seven days; urinary bladder, × 375. Small artery showing partial fibrosis of its wall. *C*, Dog 47, which survived seven days; stomach, × 400. Arteriole in submucosa of stomach resembling the example in B.

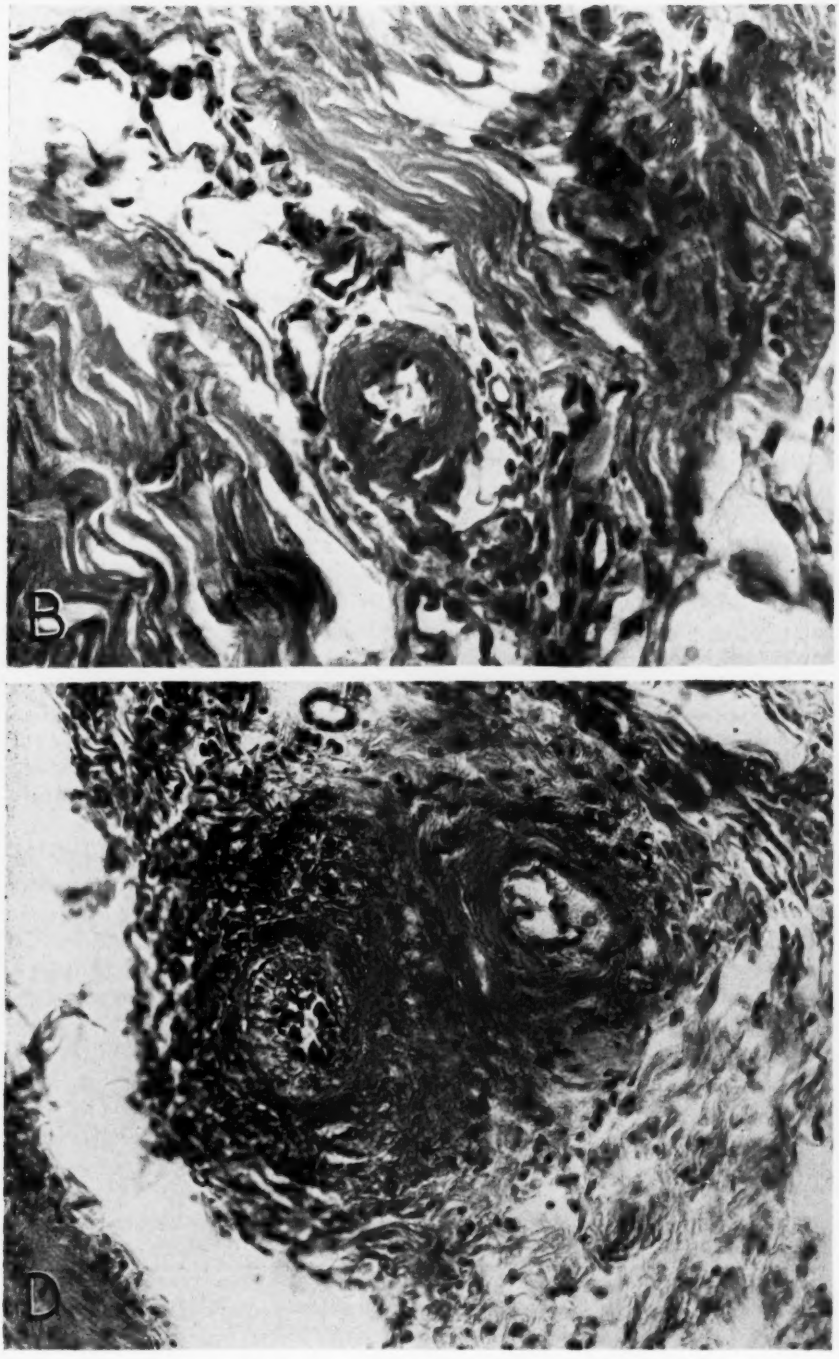


Fig. 6 (Part 2).—*B*, Dog 63, which survived nine days; skin, × 425. Arteriole in skin displaying a necrotic and hardened media which is fusing and assuming appearance of hyaline. *D*, Dog 136, which survived 14 days; stomach, × 300. Small arteries in submucosa of stomach showing necrosis and attenuation of media and deposition of a loose, fibrillar, connective tissue between endothelium and necrotic media.

puncture and a mercury manometer. The changes in the mean blood pressure have been classified into three ranges: (1) no significant change in the mean arterial pressure (0 to +20 mm. Hg), (2) a moderate hypertension (+21 to +35 mm. Hg), and (3) a severe hypertension (+40 to +90 mm. Hg). Within the first two survival groups (6 to 9 days' and 10 to 24 days' survival) 43 and 30% of the animals, respectively, revealed no significant hypertension; 20 and 18%, respectively, showed a moderate hypertension, and 37 and 52%, respectively, had a severe hypertension. This spread in the frequency of sustained hypertension afforded a more significant evaluation of the role of hypertension in the development of the cardiovascular lesions. When hypertension developed it did so by a stepwise increment in pressure during the first four to seven days. Thereafter the hypertension remained constant until shortly before death. Consequently, when present, hypertension became a sustained factor.

It is evident from Table 3 that cardiovascular lesions occurred in the absence of hypertension as well as in the presence of varying grades of hypertension. Hypertension, therefore, was not a necessary factor for the genesis of the cardiovascular injury. However, the data in Table 3, especially the total figures for the three categories of changes in blood pressure, indicate a greater incidence of cardiovascular lesions when hypertension existed. Thus, arterial lesions were observed in 35% of the 17 animals without hypertension, in 45% of the 9 animals with a moderate hypertension, and in 65% of 31 animals having a severe hypertension, and myocardial lesions were observed in 20% of the 15 animals without hypertension, in 78% of the 9 animals with a moderate hypertension, and in 68% of the 28 animals with a severe hypertension. It is evident that hypertension, although not essential for the development of the lesions, was associated with an aggravation of the lesions, either because hypertension made more severe the already existing vascular disease or because the development of hypertension was associated with factors which concomitantly increased the vascular disease.

2. Survival of Dogs Following Ablation of Renal Tissue, Incidence of Cardiovascular Lesions as Related to Survival Time, and Various Methods for Extending Survival of Nephrectomized Dogs.—Table 4 relates the incidence of myocardial lesions (necrosis and/or fibrosis) and Table 5 relates the incidence of arterial-arteriolar lesions (necrosis, early hyalinization, hyalinization, fibrosis) of the present series of dogs and of dogs which constituted the basis of former reports.[9] The survival periods have been divided into three main groups: (1) 3 to 6 days, (2) 6 to 10 days, and (3) over 10 days. These groups were placed in five categories according to type of management: (1) a group subjected to no dialysis and allowed to die early; (2) dogs subjected to dialysis by an artificial kidney of the Kolff type every three to four days; (3) dogs subjected to peritoneal irrigation twice daily, the peritoneal fluid being removed after 8 and 16 hours, respectively; (4) dogs subjected to peritoneal irrigations three times daily, and (5) dogs subject to three peritoneal irrigations daily plus a homogenous renal transplant on the 8th to 14th day.

Myocardial Lesions (Table 4): Dogs surviving over six days yielded a greater frequency of detectable myocardial lesions than animals surviving three to six days. One or two periods of dialysis by the artificial kidney, as compared with no dialysis, did not alter the incidence of these lesions in the group surviving three to six days.

TABLE 3.—*Relation of Arterial Hypertension, Expressed as Elevation of Mean Arterial Pressure over Control Value in Mm. Hg, and Incidence of Cardiovascular Lesions*

Survival Group	No. of Dogs	Increment of Blood Pressure, Mm. Hg	Arterial Lesions				Cardiac Lesions			
			None	Rare	Common	Total with Lesions	None	Microscopic	Gross and Microscopic	Total with Lesions
I. 6-9 days	16	0-20	3	3	1	4	4	1	2	3
		21-30	2	0	1	1	0	3	0	3
		40-70	2	1	3	4	3	2	1	3
II. 10-24 days	33	0-20	8	2	0	2	8	0	0	0
		21-35	3	2	1	3	2	2	2	4
		40-90	5	6	6	12	4	9	1	10
III. 15-38 days; renal transplant	8	30-65	4	2	2	4	2	5	1	6
Total	57	0-20	11	5	1	6 (35%)	12	1	2	3 (20%)
	52	21-35	5	2	2	4 (45%)	2	5	2	7 (78%)
		40-90	11	9	11	20 (65%)	9	16	3	19 (68%)

TABLE 4.—*Incidence of Myocardial Lesions as Related to Survival and Type of Management*

Management	Survival Group, Days	No. of Dogs	Lesions				
			None	Microscopic	Gross and Microscopic	Total with Lesions	
						No.	%
No dialysis	3- 6	24	13	5	6	11	46
Artificial kidney	3- 5	12	7	1	4	5	41.5
	6- 9	37	12	13	12	25	66
Peritoneal irrigation, 2 ×	10-69	23	11	5	7	12	52
Peritoneal irrigation, 3 ×	6- 9	16	7	5	4	9	56
	10-24	20	6	11	3	14	70
Peritoneal irrigation; homogenous renal transplant	15-38	8	2	5	1	6	75
	3- 6	36	20	6	10	16	44
	6- 9	53	19	18	16	34	64
	10-69	51	19	21	11	32	63

TABLE 5.—*Incidence of Arterial (Arteriolar) Lesions as Related to Survival and Type of Management*

Management	Survival Group, Days	No. of Dogs	Lesions				
			None	Rare	Common	Total with Lesions	
						No.	%
No dialysis	3- 6	24	16	5	3	8	33
Artificial kidney	3- 5	12	8	2	2	4	33
	6- 9	37	11	16	10	26	65
Peritoneal irrigation, 2 ×	10-69	23	12	4	7	11	47
Peritoneal irrigation, 3 ×	6- 9	16	6	2	8	10	62
	10-24	23	8	8	7	15	65
Peritoneal irrigation; homogenous renal transplant	15-38	8	4	2	2	4	50
Total	3- 6	36	24	7	5	12	33
	6- 9	53	17	18	18	36	68
	10-69	54	24	14	16	30	56

In the groups surviving beyond six days the incidence of cardiac lesions varied between 52 and 75%. The lowest figure was obtained for the group surviving 10 to 69 days and subjected to two peritoneal irrigations daily. The over-all incidence of myocardial lesions when computed without regard to the type of dialyzing procedure indicate no difference in frequency between the 53 dogs surviving 6 to 10 days and the 51 dogs surviving 10 to 69 days.

In Table 4 an additional breakdown of the myocardial lesions is based on the size of the lesions, that is, whether small (microscopic) or large (gross as well as microscopic). There was little difference in the frequency of these two types, except possibly in the groups having three or more peritoneal irrigations daily, which yielded mainly smaller, microscopic foci of myocardial injury.

Arterial Lesions (Table 5): The incidence of arterial lesions was similar to that of myocardial lesions. The groups surviving three to six days revealed a lower frequency of vascular lesions than the various groups surviving over six days, an observation similar to that in relation to the heart. Also, in the three to six day survival group, one or two periods of dialysis with the artificial kidney did not alter the incidence of lesions as compared with that of the group having no dialysis. The groups surviving beyond six days yielded incidences of vascular lesions varying between 47 and 65%. The lowest figure was obtained for the group subjected to two peritoneal irrigations daily. As with the cardiac lesions, a grouping of the animals according to survival but irrespective of the dialyzing procedure indicates no outstanding difference in incidence of lesions between the 53 dogs surviving 6 to 9 days and the 54 dogs surviving 10 to 69 days.

In Table 5 the incidence of vascular lesions is also broken down into rare lesions, namely, those seen in one or two sites only, and common lesions, seen in three or more sites scattered in the body. As indicated in the table, there was a fairly equal distribution of this subclassification within the various groups. The characteristics of the lesions varied with time; beyond 10 days there was a tendency toward a hyaline appearance and the presence of connective-tissue elements in the arterial wall.

A similarity existed between the incidence and the character of the myocardial and arterial lesions in the various groups. This relationship may be considered as an additional indication of the primary nature of the myocardial injury, since the plausible explanation for it involves the fact that both the myocardial fibers and the fibers of the media of small arteries and arterioles are susceptible to the same injurious factor(s).

3. *Volume of Fluid Used in Peritoneal Irrigation and Incidence of Cardiovascular Lesions.*—An attractive explanation for the uremic cardiovascular lesions of the dog is based on the possibility that the toxic factor(s), ordinarily excreted or otherwise metabolized by the kidney, accumulates within the body, thus damaging the heart and arteries. Should such substances be filtrable, the dialyzing procedures would remove them from the body and thereby protect the heart and arteries from injury. One method of evaluating this possibility is to measure the amount of fluid removed each day from the peritoneal cavity after equilibration with the body fluids. This type of appraisal was effected in the present series of dogs by measuring the volume of fluid introduced into and removed from the peritoneal cavity during each irrigating procedure. The amount of fluid recovered

has been expressed as the amount removed per 24 hours per kilogram of body weight. The initial body weight was used throughout.

In Tables 6 and 7, the incidence of myocardial and arterial (arteriolar) lesions, respectively, has been related to the volume of fluid recovered. The dogs are classi-

TABLE 6.—*Incidence of Myocardial Lesions as Related to Average Volume of Fluid Removed from Peritoneum* *

Survival Group	No. of Dogs	Type of Lesion	140-199 Cc./Kg./ 24 Hr.	200-299 Cc./Kg./ 24 Hr.	300-500 Cc./Kg./ 24 Hr.	Total No. of Dogs
I. 6-9 days	16	None	2	2	3	7
		Microscopic	0	4	2	6
		Gross and microscopic	3	0	0	3
II. 10-24 days	28	None	7	5	2	14
		Microscopic	1	7	3	11
		Gross and microscopic	0	2	1	3
III. 15-38 days; renal transplant	9	None	0	2	0	2
		Microscopic	1	1	3	5
		Gross and microscopic	0	1	0	1
Total	52	None	9	9	5	23
		Microscopic	2	12	8	22
		Gross and microscopic	3	3	1	7
No lesions			9	9	5	23
Lesions			5 (36%)	15 (62%)	9 (64%)	29 (56%)

* Expressed as cubic centimeters per kilogram of body weight per 24 hours.

TABLE 7.—*Incidence of Arterial (Arteriolar) Lesions as Related to Average Volume of Fluid Removed from Peritoneum* *

Survival Group	No. of Dogs	Type of Lesion	140-199 Cc./Kg./ 24 Hr.	200-299 Cc./Kg./ 24 Hr.	300-500 Cc./Kg./ 24 Hr.	Total No. of Dogs
I. 6-9 days	16	None	1	4	2	7
		Rare	1	2	1	4
		Common	3	0	2	5
II. 10-24 days	32	None	6	6	3	15
		Rare	3	5	2	10
		Common	0	6	1	7
III. 15-38 days; renal transplant	8	None	1	2	1	4
		Rare	0	0	2	2
		Common	0	2	0	2
Total	56	None	8	12	6	26
		Rare	4	7	5	16
		Common	3	8	3	14
No lesions			8	12	6	26 (46%)
Lesions			7 (47%)	15 (55%)	8 (57%)	30 (54%)

* Expressed as cubic centimeters per kilogram of body weight per 24 hours.

fied into three groups according to survival period, 6 to 9 days, 10 to 24 days, and 15 to 38 days; the last group had the addition of a homogenous renal transplant. The dogs were also classified according to frequency of lesions in relation to three ranges of fluid volume recovered per day per kilogram of body weight, namely 140 to 199 cc., 200 to 299 cc., and 300 to 500 cc. Dogs in the latter two categories had substantial quantities of fluid removed from the body.

Myocardial Lesions: Table 6 shows a scattering of animals with and without lesions within the survival groups and among those with the three magnitudes of fluid removed from the peritoneal cavity per day.

Among the 52 animals listed in Table 6 in the three survival groups, the incidence of myocardial lesions amounted to 56%, 50%, and 75%, respectively. However, in the 6 to 9 day group 6 of the 9 animals with lesions were in the higher-volume categories, in the 10 to 24 day group 13 of the 14 animals with lesions were in the higher-volume categories, and in the 15 to 38 day group 5 of the 6 animals with lesions were in the higher-volume categories. When all the animals in the volume categories are included, it may be observed that 5 out of 14 (36%) in the least-volume category and 15 of 24 (62%) and 9 of 14 (64%) in the greater-volume categories had lesions. From these data it appears that the recovery of 140 to 199 cc. of peritoneal lavage fluid per kilogram per day was as protective, and possibly more so, against the development of myocardial lesions as the recovery of 1.5 to 2.5 times these amounts.

Arterial Lesions: In Table 7 a scattering of arterial lesions within the survival groups and volume categories can be noted, as in the case of cardiac lesions. Data concerning the relation of fluid removed to the incidence of lesions were similar. Thus, in the 6 to 9 day survival group 5 of 9 animals with lesions were in the higher-volume categories; in the 10 to 24 day survival group 14 of 17 animals with lesions were in the higher-volume categories, and in the 15 to 38 day survival group all animals with lesions were in the higher-volume categories. As in the case of the heart, the higher recovery of peritoneal fluid per day did not lower the frequency of arterial lesions and may have increased it.

4. *Level of Retention of Nitrogenous Waste Products in Body Fluids and Incidence of Cardiovascular Lesions.*—The retention of nitrogenous waste products was gauged by the concentration of urea in the blood and the concentration of urea in the peritoneal fluid after its equilibration with the body fluids as determined by the urea concentration in the pool of fluid removed in each 24-hour period. The blood urea concentration was determined on a morning sample after the longest interval of retainment of fluid within the peritoneal cavity and represented the highest urea level in the 24-hour period.

Tables 8, 9, and 10 relate respectively the incidence of cardiovascular lesions in each survival group as related to the mean blood urea concentration after the nephrectomies, the range of the blood urea concentration, and the mean concentration of urea in the pooled batches of peritoneal fluid recovered during each 24 hours.

As noted in Table 8, there was no outstanding correlation between the level of blood urea, as determined, and the incidence of arterial and myocardial lesions. Thus, among the dogs having a mean blood urea level varying between 50 and 200 mg. per 100 cc., 36% (25 dogs) showed arterial and 52% (24 dogs) myocardial lesions, whereas among the dogs having a mean urea level between 201 and 450 mg. per 100 cc., 54% (27 dogs) yielded vascular and 61% (23 dogs) myocardial lesions. These findings indicate that the level of blood urea did not reflect the effectiveness of the mechanism evoking the cardiovascular lesions.

Additional support for this conclusion is gained from the data in Tables 9 and 10. Table 9 reveals no outstanding correlation between the various ranges of blood urea concentration after the nephrectomies and the incidence of cardiovascular lesions.

TABLE 8.—*Mean Blood Urea Concentration Following Bilateral Nephrectomy and Its Relation to Incidence of Cardiovascular Lesions*

Survival Group	No. of Dogs	Average No. Urea Values	Mean Urea Concentration, Mg./100 Cc.	Arterial Lesions				Cardiac Lesions			
				None	Rare	Common	Total with Lesions	None	Microscopic	Gross and Microscopic	Total with Lesions
I. 6-9 days	13	3	140-200	4	2	1	3	4	2	1	3
			201-306	2	0	4	4	2	2	2	4
II. 10-24 days	31	4	100-200	8	1	2	3	5	4	1	5
	26		201-300	9	5	2	7	6	5	1	6
			301-450	2	0	2	2	1	2	1	3
III. 15-38 days; renal transplant	8	10	50-100	2	2	1	3	2	3	0	3
			101-200	2	0	0	0	0	2	0	2
			201-450	0	0	1	1	0	0	1	1
Total	52		50-200	16	5	4	9 (36%)	11	11	2	13 (54%)
	47		201-450	13	5	9	14 (52%)	9	9	5	14 (61%)

TABLE 9.—*Range of Blood Urea Concentration After Bilateral Nephrectomy and Its Relation to Incidence of Cardiovascular Lesions*

Survival Group	No. of Dogs	Range of Urea Concentration, Mg./100 Cc.	Arterial Lesions				Cardiac Lesions			
			None	Rare	Common	Total with Lesions	None	Microscopic	Gross and Microscopic	Total with Lesions
I. 6-9 days	13	50-150 to 165-300	4	2	1	3	3	3	1	4
		151-230 to 300-420	3	0	4	4	3	1	2	3
II. 10-24 days	34	50-150 to 165-314	8	5	3	8	7	7	2	9
	28	151-230 to 175-560	6	2	2	4	4	1	1	2
		231-400 to 240-560	3	1	1	2	2	3	0	3
III. 15-38 days; renal transplant	7	30-80 to 150-350	4	2	1	3	2	5	0	5
Total	54	30-150 to 165-350	16	9	5	14 (47%)	12	15	3	18 (60%)
	48	151-400 to 175-560	11	3	7	10 (48%)	9	5	3	8 (47%)

TABLE 10.—*Mean Concentration of Urea in Pooled Twenty-Four Hour Outflow Fluid from Peritoneum and Its Relation to Incidence of Cardiovascular Lesions*

Survival Group	No. of Dogs	Mean Urea Concentration, Mg./100 Cc.	Arterial Lesions				Cardiac Lesions			
			None	Rare	Common	Total with Lesions	None	Microscopic	Gross and Microscopic	Total with Lesions
I. 6-9 days	12	100-200	4	2	2	4	4	2	2	4
		201-300	0	1	3	4	2	1	1	2
II. 10-24 days	25	100-200	2	0	2	2	2	1	1	2
	22	201-300	8	6	3	9	7	7	2	9
		301-355	1	1	2	3	1	1	0	1
Total	37	100-200	6	2	4	6 (50%)	6	3	3	6 (50%)
	34	201-355	9	8	8	16 (64%)	10	9	3	12 (55%)

Finally, Table 10 discloses no significant correlation between the mean urea concentration of the peritoneal fluid recovered daily from the peritoneal cavity after renal ablation and the occurrence of cardiovascular lesions. Figures for the latter are more representative of the mean urea concentration in body fluids over each 24-hour period, since the pooled outflow fluid was in equilibrium with body fluids throughout the 24 hours.

5. *Total Quantity of Urea Removed from Body, Expressed as Grams per Kilogram of Body Weight, and Incidence of Cardiovascular Lesions.*—By determining the daily volume of peritoneal fluid recovered and its urea concentration, the total

TABLE 11.—*Total Quantity of Urea Removed from Body Following Second Nephrectomy* as Related to Incidence of Cardiovascular Lesions*

			Arterial Lesions				Cardiac Lesions			
Survival Group	No. of Dogs	Urea, Gm./Kg.	None	Rare	Common	Total with Lesions	None	Microscopic	Gross and Microscopic	Total with Lesions
I. 6-9 days	12	2-4.9	3	2	4	6	5	1	3	4
		5-8.9	1	1	1	2	1	2	0	2
II. 10-24 days	28	2-4.9	5	0	2	2	6	0	1	1
		5-8.9	5	9	2	11	7	6	1	7
		9-12	2	0	3	3	0	3	1	4
Total	40	2-4.9	8	2	6	8 (50%)	11	1	4	5 (31%)
	37	5-8.9	6	10	3	13 (69%)	8	8	1	9 (53%)

* Expressed as grams per kilogram of body weight.

TABLE 12.—*Changes in Body Weight as Related to Incidence of Cardiovascular Lesions*

			Arterial Lesions				Cardiac Lesions			
Survival Group	No. of Dogs	Change in Body Wt., Kg.	None	Rare	Common	Total with Lesions	None	Microscopic	Gross and Microscopic	Total with Lesions
I. 6-9 days	15	−1.5 to 0	5	3	2	5	4	5	1	6
		+0.5 to +1.8	2	1	2	3	3	1	1	2
II. 10-24 days	31	−2.5 to 0	8	5	5	10	6	7	3	10
	27	+0.5 to +3.8	7	4	2	6	8	3	0	3
Total	46	−2.5 to 0	13	8	7	15 (53%)	10	12	4	16 (61%)
	42	+0.5 to +3.8	9	5	4	9 (50%)	11	4	1	5 (31%)

quantity of urea removed from the body via this route during the period of survival was obtained. The relationship of this quantity, expressed as grams of urea per kilogram of weight, to the lesions is shown in Table 11.

There seems to be no outstanding correlation between the quantity of urea removed from the body and the incidence of cardiovascular lesions. A lower figure was obtained for cardiac lesions in the group associated with a recovery of smaller amounts of urea, but this was offset by the higher figure for arterial lesions in the same group. The recovery of urea may be considered as indicating the degree of protein breakdown, or body wastage. The observation in Table 11 minimizes the influence of body wastage, as reflected by the outpouring of urea, on the rate of production of cardiovascular lesions.

6. *Changes in Body Weight and Their Relation to the Incidence of Cardiovascular Lesions.*—The body weight was determined each morning after the withdrawal of the overnight volume of peritoneal fluid. The data depicting the relation of weight changes to the lesions are tabulated in Table 12. Weight gain resulted from the accumulation of fluid in the body as indicated by the lack of complete recovery of fluid from the peritoneal cavity and the development of overt edema in some animals. Weight loss apparently resulted primarily from wastage of body substance. Whether there was a relative gain in fluid within the body in those animals whose weight decreased or remained unchanged was not determined in the present series.

The data in Table 12 indicate a lack of correlation between substantial changes in body weight and the incidence of cardiovascular lesions. Of the 28 animals which lost weight or had no change in weight 53% yielded arterial (arteriolar) lesions, and of those gaining weight 50% revealed arterial lesions. Of 26 animals losing weight or remaining unchanged 61% showed myocardial lesions, and of 16 animals gaining weight 31% had cardiac lesions. It is concluded that the accumulation of fluid within the body, mainly within the extracellular space, did not accelerate the rate of production of cardiovascular lesions following the nephrectomies and that wastage of the body within the limits observed likewise did not accentuate the incidence of cardiovascular lesions.

7. *Changes in Blood and Red Cell Volume and Their Relation to Cardiovascular Lesions.*—The relationship of the incidence of cardiovascular lesions and the total blood volume and red blood cell mass as determined by the T-1824 dye technique is expressed in Tables 13 and 14. These tables demonstrated that no difference in the frequency of lesions was detected between groups showing slightly positive to slightly negative changes in blood and red cell volume and the groups with pronounced negative changes in these volumes. Thus the development of hypovolemia and a prominent anemia did not appear to alter the rate of development of the cardiovascular lesions.

8. *Homogenous Renal Transplants.*—The introduction of homogenous renal transplant 8 to 14 days after the second nephrectomy did not alter the incidence of the cardiovascular lesions. By surviving longer than the other groups, the animals revealed a greater proportion of reparative changes within the lesions.

COMMENT

The cardiovascular lesions of the dog following bilateral nephrectomy result from injury of the cardiac muscle and of the smooth muscle of the media of small arteries and arterioles and the reparative changes which the injury stimulates. A spectrum of changes is observed from necrosis to fibrosis of the heart and sclerosis of the arteries. Demonstration of the healed sclerotic phase of the vascular lesions has resulted mainly from the prolongation of life of the animals by means of dialyzing procedures. The myocardial injury is a direct one, as indicated by the equal frequency of cardiac and of vascular lesions and, more emphatically, by the dissociation of the occurrence of cardiac necrosis and fibrosis and lesions of small coronary arteries and arterioles. It is evident that the cardiovascular lesions in these experiments should be considered as one entity and that emphasis should not be confined to the vascular lesions.

The arteriolar necrosis and fibrosis of the dog following bilateral nephrectomy are similar to certain lesions encountered in the human in malignant hypertension.[10] Moreover, human beings with malignant hypertension show myocardial necrosis and microscopic scars for which there has not been an entirely satisfactory and conclusive explanation. Interest in the canine lesions is further heightened by the occurrence of severe hypertension in a high proportion of animals following nephrectomy under the conditions of the experiments herein reported. Although these similarities between the human and experimental diseases do not necessarily indicate an equal causative background, they nevertheless call for further probing into the experimental preparation.

The experimental data support conclusively the view that hypertension is not essential for the development of the cardiovascular lesions, for 35% of the animals without hypertension revealed the same lesions as those with hypertension. However, the greater incidence of lesions among the hypertensive dogs indicated an aggravating influence associated with, but not necessarily causally related to, the presence of the elevated blood pressure. These conclusions are not in accord with the views of Wilson and Pickering,[11] Wilson and Byrom,[11] and Byrom and Dodson,[11] which consider hypertension as the sole requisite for such lesions, but they are in concord with the contention of Goldblatt [1e] that hypertension alone is not sufficient for the development of arteriolar necrosis when the usual experimental techniques for evoking hypertension are used. The aggravation of the cardiovascular lesions of the experimental preparation in association with hypertension may have its counterpart in human malignant hypertension, in which it has been shown that certain procedures affecting a lowering of the blood pressure may ameliorate the progress of the cardiovascular complications.

A preeminent role of the kidney in the genesis of the cardiovascular lesions under consideration is suggested further by the occurrence of similar lesions following renal manipulations other than bilateral nephrectomy. Similar lesions following manipulations such as the ligation of both ureters, the ligation of one ureter followed by removal of the opposite kidney, the implantation of the ureter into the small bowel followed by contralateral nephrectomy, the implantation of the ureter into the inferior vena cava and contralateral nephrectomy, and the sectioning of both ureters so as to permit the free flow of urine into the peritoneal cavity have been described in reports from this institution.[1b] All these procedures not only stop the flow of urine to the outside of the body but are also associated with a tendency toward damage of renal tubules. Cardiovascular lesions similar to those which follow these various insults to the kidney have been observed by other workers as a result of other types of renal injury, such as the extreme narrowing of the renal artery by a Goldblatt clamp,[1e] occlusion of the renal artery with infarction of the kidney,[1g] and renal injury by mercury and other agents.[1h] That the phenomenon is not species specific has been demonstrated by the occurrence of similar lesions following similar renal

10. Muirhead, E. E., and Montgomery, P. O'B.: Unpublished data.

11. Byrom, F. B., and Dodson, L. F.: The Causation of Acute Arterial Necrosis in Hypertensive Disease, J. Path. & Bact. **60**:357, 1948.

insults in the rabbit [11] and the rat.[12] Thus certain renal functions appear to be essential for the integrity of the heart and arteries.

How the kidney discharges functions which prevent these experimentally demonstrable cardiovascular lesions is not known. Three hypotheses appear attractive: (1) the toxic concept, which implicates the retention within the body of cardiotoxic and vasotoxic substances which are normally excreted by the kidneys; (2) the electrolytic concept, emphasizing compositional changes of intracellular electrolytes which the kidney normally helps to maintain within rigid bounds, and (3) the metabolic concept, which entails a consideration of internal functions by the kidney, other than those concerned in the excretion of urine, which might be concerned with the metabolism of the heart and blood vessels.

The present study serves to elucidate certain features of the toxic theory. Increasing the frequency of peritoneal irrigations from two to three times daily did not lower the incidence of lesions. Increasing the daily irrigations to copious levels on a body-weight basis not only failed to decrease the incidence of lesions but may have increased it. From a theoretical view, the expansion of body fluids has been considered as a means of diluting toxins in uremia; [13] however, animals gaining considerable weight as a result of expansion of body fluids had lesions as often as animals which either gained no weight or lost weight. These observations appear to oppose the view that a readily diffusible toxin accumulates within the body fluids. It is conceivable, in view of these findings, that a poorly diffusible toxin, one which might require the action of a tubular transport mechanism for the major portion of its excretion by the kidney, accumulates within the body. No data bearing directly on this possibility have been obtained. Such a hypothetical toxin would seem to have no constant relationship to the level of retention of urea.

The electrolytic concept requires consideration as a result of the occurrence of cardiovascular lesions resembling those which follow bilateral nephrectomy after experimental procedures, such as the administration of desoxycorticosterone acetate and a high sodium chloride intake,[14] which are known to increase the sodium content and decrease the potassium content of various tissues, especially muscle. Moreover, in some species this procedure evokes a severe hypertension.[14a] Also, it has been demonstrated that other experimental manipulations of the kidney which evoke hypertension likewise cause an increase in the sodium and a decrease in the potassium content of muscular tissues.[15] The hypertension following bilat-

12. Toussaint, C.: Les modifications pathologiques provoquées par l'ischémie partielle du rein, l'hydronéphrose bilatérale et la nephrectomie totale chez le rat intact et chez le rat surrénalectomisé, Rev. belge path. et méd. expér. **21**:465, 1952. Lendingham, J. M.: Nature of Hypertension Occurring in Nephrectomized Parabiotic Rat, Clin. Sc. **10**:423, 1951.

13. Hoffman, W. S., and Marshall, D.: Management of Lower Nephron Nephrosis: Report of 6 Cases, Arch. Int. Med. **83**:249, 1949. Barry, F. S.; Shafton, A. L., and Ivy, A. C.: Experimental Edema in Nephrectomized Dogs: Rôle of Water and Chlorides, ibid. **51**:200, 1933.

14. (*a*) Selye, H.; Hall, C. E., and Rowley, E. M.: Malignant Hypertension Produced by Treatment with Desoxycorticosterone Acetate and Sodium Chloride, Canad. M. A. J. **49**:88, 1943. (*b*) Masson, G. M. C.; Hazard, J. B.; Corcoran, A. C., and Page, I. H.: Experimental Vascular Disease Due to Desoxycorticosterone and Anterior Pituitary Factors, Arch. Path. **49**:641, 1950.

15. Eichelberger, L.: Distribution of Water and Electrolytes Between Blood and Skeletal Muscle in Experimental Hypertension, J. Exper. Med. **77**:205, 1943. Laramore, D. C., and Grollman, A.: Water and Electrolyte Content of Tissues in Normal and Hypertensive Rats, Am. J. Physiol. **161**:278, 1950.

eral nephrectomy has been considered [16] to be associated with the expansion of body fluids through the retention of sodium. The present data, however, indicate that hypertension is not essential for the development of the lesions. Moreover, the incidence of lesions in the group of animals showing an overt expansion of body fluids, as indicated by a rapid gain in body weight and obvious edema, was no greater than the incidence in the group which exhibited no edema and either had no change in weight or lost weight. It is appreciated that the latter group may have experienced a relative gain in fluid even though the body weight declined; nevertheless, the marked disparity between these two groups suggests that the

TABLE 13.—*Changes in Blood Volume and Incidence of Cardiovascular Lesions*

			Arterial Lesions				Cardiac Lesions			
Survival Group	No. of Dogs	Changes in Blood Volume, %	None	Rare	Common	Total with Lesions	None	Microscopic	Gross and Microscopic	Total with Lesions
6-9 days	8	+13 to −20	3	1	2	3	2	3	1	4
		−24 to −30	0	2	0	2	1	1	0	1
10-24 days	20	+30 to −20	5	3	3	6	3	4	2	6
	18	−28 to −56	4	2	3	5	4	4	1	5
Total.....	28	+30 to −20	8	4	5	9 (53%)	5	7	3	10 (66%)
	26	−24 to −56	4	4	3	7 (63%)	5	5	1	6 (54%)

TABLE 14.—*Changes in Red Blood Cell Volume and Incidence of Cardiovascular Lesions*

			Arterial Lesions				Cardiac Lesions			
Survival Group	No. of Dogs	Change, R. B. C. Volume, %	None	Rare	Common	Total with Lesions	None	Microscopic	Gross and Microscopic	Total with Lesions
6-9 days	8	+14 to −20	2	2	1	3	2	3	0	3
		−38 to −82	1	1	1	2	1	1	1	2
10-24 days	21	0 to −20	4	4	2	6	2	5	1	6
	19	−28 to −75	5	2	4	6	5	4	2	6
Total.....	29	+14 to −20	6	6	3	9 (60%)	4	8	1	9 (69%)
	27	−28 to −82	6	3	5	8 (57%)	6	5	3	8 (57%)

interstitial accumulation of fluids is not the determining factor in the genesis of the lesions.

A consideration of the anatomic make-up of small arteries and arterioles and the study of these vessels during the various evolutionary steps in the pathogenesis of the lesions dispel the role of mere expansion of the extracellular fluid space as a cause of the lesions. Edema of the veil-like intima was not observed during the present studies. The interstitial accumulation of fluid within the "brick and

16. Braun-Menendez, E.: Blood Volume and Extracellular Fluid Volume in Experimental Hypertension, in Hypertension, edited by E. T. Bell, Minneapolis, University of Minnesota Press, 1951, p. 98. Leonards, J. R., and Heisler, C. R.: Artificial Kidney: Maintenance of Life in Bilaterally Nephrectomized Dogs and Its Relation to Malignant Hypertension, Am. J. Physiol. **167**:553, 1951. Twiss, E. E., and Kolff, W. J.: Treatment of Uremia by Perfusion of an Isolated Intestinal Loop: Survival for 46 Days After Removal of the Only Functioning Kidney, J. A. M. A. **146**:1019, 1951.

mortar" arrangement of the media appears most difficult and has likewise not been detected. Edema of the adventitia has been encountered in certain sites, such as the submucosa of the gastrointestinal tract, but edema of the adventitia of certain blood vessels occurs in various edematous states, both in experimental preparations and in human diseases, without the occurrence of vascular lesions. Moreover, edema does not explain the myocardial necrosis which is an intimate part of the pathologic picture. It seems apparent that the cardiovascular lesions in these experimental preparations do not result from the enlargement of the extracellular fluid space but represent a reflection of a fundamental disturbance within the muscle fibers of the heart and the media of small arteries and arterioles. Yet, the electrolytic concept, in the sense of compositional changes within the muscle, needs further attention. The only observation in the present study which might be related to such a disturbance was the observation that an increase in the volume of peritoneal fluid on a body-weight basis during the dialyzing procedure appeared to increase the frequency of lesions.

The metabolic concept is considered mainly because those procedures which are followed by cardiovascular lesions are associated either with the absence of renal tissue or with a tendency toward injury of renal tubules. Thus it might be considered that in the absence of renal tissue or as a result of renal injury there is a deficiency of substances elaborated by the kidney which are necessary for the integrity of the heart and arteries. The present study yielded no direct information on this possibility.

These conclusions may be drawn: 1. The cardiovascular lesions following bilateral nephrectomy of the dog result from necrosis of the heart and arteries, which is followed in time by reparative changes. 2. Hypertension is not essential for the development of these lesions. The occurrence of hypertension is associated with a significant increment in the incidence of the lesions. 3. The lesions occur in the absence of excessive retention of fluid in the body as judged by fluid-balance studies and the body weight.

The role of several additional factors in the incidence of the lesions has been considered. The data have been discussed in relation to the three most attractive concepts of pathogenesis of the lesions, namely the toxic, electrolytic, and metabolic concepts.

Case Reports

PLEUROPULMONARY TULAREMIA COMPLICATED BY PERIPHERAL NEURITIS

MORTIMER RAPHAEL, M.D.
AND
AUGUSTUS E. ANDERSON, M.D.
NEW ORLEANS

SINCE the discovery of Pasteurella tularensis by McCoy [1] in 1910 and the demonstration that it produces disease in man, as reported by Francis [2] in 1922, tularemia has been found masquerading in many forms. These have been classified as ulceroglandular, oculoglandular, glandular, and typhoidal; occasionally are added pleuropulmonary and oral-abdominal forms.

Initial pathologic changes occur at the site of inoculation of the organism, and a bacteremia soon follows. The organism then appears to have a predilection for lodging in the lungs, liver, spleen, and lymph nodes. Following the septicemia, neurological symptoms and signs may appear, the most frequent being nonspecific phenomena; i. e., delirium, stupor and restlessness. These have been attributed to the severe septic or toxic state induced by the organism. The next most frequent neurological complication is lymphocytic meningitis.[3] Finally, there have been two reported cases of encephalitis.[4] The case of tularemia reported here is unusual in that the patient had peripheral neuritis, a heretofore unreported complication of the disease.

REPORT OF CASE

History.—J. H. (28,105), a 42-year-old Negro, was admitted to the Veterans Administration Hospital, New Orleans, on Jan. 3, 1952, complaining of a "bad cold" of 17 days' duration. His first symptom had been malaise followed by generalized weakness, which had progressed until he was unable to work efficiently as a woodcutter. He later began having chilly sensations, fever, sweats, and pleuritic pain in the right side of the chest. A cough developed which produced

From the Medical Service, Veterans Administration Hospital, and the Department of Medicine, The Tulane University of Louisiana School of Medicine.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. McCoy, G. W.: A Plague-Like Disease of Rodents, Pub. Health Bull. **43**:53-71, 1911.

2. Francis, E.: Tularemia Francis 1921: A New Disease of Men, J. A. M. A. **78**:1015-1018, 1922.

3. Stuart, B. M., and Pullen, R. L.: Tularemic Meningitis: Review of Literature and Report of Case with Postmortem Observations, Arch. Int. Med. **76**:163-166, 1945. Foshay, L.: Tularemia: Summary of Certain Aspects of Disease Including Methods of Early Diagnosis and Results of Serum Treatment in 600 Patients, Medicine **19**:11-83, 1940. Glass, G. B. J.: Tularemic Meningitis and Serous Meningitis, M. Clin. North America **32**:769-778, 1948.

4. Hartman, F. W.: Tularemic Encephalitis: Pathology of Acute Tularemia with Brain Involvement and Coexisting Tuberculosis, Am. J. Path. **8**:57-62, 1932. Berlin, L., and Petterson, P. D.: Tularemic Encephalitis and Neurologic Manifestations of Tularemia, Journal-Lancet. **70**:97-99, 1950.

moderate amounts of mucopurulent material. An unknown amount of weight loss had occurred. The patient was questioned repeatedly relative to contacts with the recognized vectors of tularemia, but he denied such contacts.

Physical Examination.—The patient was poorly nourished, weak and mentally clear; he coughed frequently and appeared mildly dyspneic at rest. Temperature was 102.8 F.; pulse rate, 98; blood pressure, 114/60. Nuchal rigidity was not present. There was diminished expansion of the right lower part of the chest; over the same area there were decreased vocal and tactile fremitus, dullness to percussion, and diminished intensity of breath sounds. Fine rales could be heard throughout the right upper part of the chest. The left side of the chest was normal on examination. The patient was unable to dorsiflex the right foot. Deep tendon reflexes were hyperactive bilaterally. In the axillary and inguinal regions there were several nontender, shotty lymph nodes varying from 0.5 to 1 cm. in diameter.

Laboratory Findings.—Roentgenologic examination of the chest revealed a diffuse haziness of the lower four-fifths of the right hemithorax with elevation of the right diaphragmatic shadow; the haziness blended laterally with an area of pleural separation. The horizontal and oblique fissures were well demonstrated. A patchy infiltration was noted throughout the visible portion of the right lower lobe and the posterior portion of the upper lobe. It was the consensus that the aforementioned findings were consistent with bronchopneumonia and pleural effusion.

The hemogram showed leucocytes, 10,500, with a differential count of 55% neutrophiles, 39% lymphocytes, 5% monocytes, and 1% cosinophiles; erythrocytes, 4,600,000, and hemoglobin, 10 gm. The hematocrit reading was 43. The sedimentation rate was 35 mm. an hour. Urinalysis gave the following results: reaction, acid; specific gravity, 1.028; albumin, 1+; test for sugar, negative. There were many hyaline and granular casts. Sputum examinations for acid-fast organisms gave negative results; cultures grew Staphylococcus aureus. Blood cultures were sterile.

Course in Hospital.—On the day of admission, the patient was subjected to a thoracentesis, and 150 cc. of straw-colored, slightly turbid fluid was removed from the right side of the chest. The fluid had a specific gravity of 1.020 and a leukocyte count of 10,500 per cubic millimeter; 75% of the leucocytes were neutrophiles, and the rest were lymphocytes. Cultures of the fluid were sterile. After thoracentesis treatment with penicillin was instituted in a dosage of 600,000 units every four hours. The next day the patient became restless, confused, disoriented, and delirious. On the third hospital day his sensorium cleared, but he continued to have daily temperature elevations ranging between 101 and 104 F. Aureomycin, 2 gm. a day, was added to the regimen on the fifth day. An electrocardiogram was made at that time, and findings were compatible with mild pericarditis. A pericardial friction rub was never heard. After treatment with aureomycin was instituted, the patient's fever subsided by lysis; within five days his temperature had become normal, and it remained so. With the subsidence of fever, there was marked symptomatic improvement. Gradual clearing of the right lung occurred, and the electrocardiogram reverted to normal.

Seven days after admission the patient complained that his foot drop was not responding and that he had weakness of the fingers of the right hand, with numbness along the ulnar aspect of the hand. Examination revealed generalized muscle weakness in the right hand and right foot drop. There were impaired perception of vibration and poorly defined loss of touch and pain sensation in the distal portions of all four extremities. Stimulation with galvanic and faradic currents revealed a partial reaction of degeneration involving the right peroneal nerve. Spinal fluid examination, x-ray pictures of the skull, and an electroencephalogram showed nothing abnormal. Because of the aforementioned neuropathies, treatment with thiamine hydrochloride was begun and physical therapy instituted.

On the 13th hospital day the serum titer for Past. tularensis was 1:640; by the 19th day it had increased to 1:5,120. Subsequent determinations ranged from 1:320 to 1:640.

Administration of penicillin was discontinued on the 20th day and of aureomycin on the 30th day. Paresthesia of the right hand gradually disappeared, and there was return of perception of pin prick, touch, and vibration. Full strength had returned to the right hand by the 30th day. Foot drop responded to therapy slowly; at the time of discharge on the 85th day the patient was barely able to dorsiflex the right foot.

COMMENT

The presence in this case of serum agglutinins for Past. tularensis in titers which rose progressively to a maximum of 1 : 5,120, is felt to confirm to a reasonable degree the diagnosis of tularemia. In addition the patient showed typical findings of peripheral polyneuritis involving motor and sensory components. Since there was a paresis of the right lower extremity prior to the institution of any form of therapy, the antibiotics, penicillin and aureomycin, can be ruled out as possible etiologic agents of the neuritis.

Cobb and Coggeshall [5] have classified generalized polyneuritis into the following etiologic types: bacteriotoxic, viral, deficiency or metabolic, and chemical. It is thought that tularemia should be added to the long list of infectious diseases which may be complicated by polyneuritis secondary to absorption of bacterial toxins.

SUMMARY

A case of pleuropulmonary tularemia complicated by peripheral neuritis and treated successfully with aureomycin is reported.

5. Cobb, S., and Coggeshall, H. C.: Neuritis, J. A. M. A. **103**:1608-1617, 1934.

Books

The Metabolic Response to Surgery. By Francis D. Moore, M.D., and Margaret R. Ball, A.B. Price, $7.50. Pp. 167, with 56 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1952.

The philosophy of this monograph is best illustrated by direct quotation: "The dangerously sick patient today is not a problem in diagnosis, sepsis, technique, pain. He is a problem in balance, in nutritional decompensation, in endocrine function, in extrarenal loss." This volume deals, then, with the patient's contribution to successful surgery—his biologic response to surgery.

A large mass of carefully collected metabolic balance data on nitrogen, potassium, sodium, and calories is clearly presented in the explanatory texts and numerous charts. The theories of the catabolic response to injury are analyzed briefly, followed by a detailed consideration of the role of starvation, immobilization, and endocrine (adrenal cortex) factors in this response. Interesting control experiments on college students, including general anesthesia and mock operations, are described, and the analogies and differences between the metabolic processes of surgical trauma and the artificial combination of short-term starvation, immobilization, and administration of corticotropin (ACTH) are indicated. The important influence of nutritional depletion, so prevalent in chronic illness, in modifying the metabolic response to single or repeated surgical trauma is well covered. There is a good discussion in Chapter 4 on potassium loss, hypokalemia, and associated alkalosis, with, again, appropriate control experiments on volunteers. Separate chapters are devoted to the metabolic responses after complicated gastrointestinal surgery, extensive burns, and adrenalectomy. There are interesting observations on the relation between caloric and nitrogen intake and between the need for, and the utilization of, nitrogen in Chapter 6, which deals with the metabolic balance effects of intravenous administration of protein hydrolysates, serum albumin, and red cell transfusions.

For the general physician who may shy away from metabolic charts, Chapter 7 presents a very readable summary of the authors' concepts and facts. The normal pattern of metabolic response to surgery is outlined, along with the variations in the type of response pattern—excessive, depletion, hypoadrenal and extrarenal. There is sound advice on appropriate treatment, with emphasis, as well, on what should not be done.

There is an appendix on surgical diets and parenteral supplements. An adequate bibliography concludes the book.

This volume is a fine example of the scientific spirit of modern surgery. It contains a great deal of information of interest and value to physicians and investigators concerned with the role of nutrition and metabolism in response to stress.

Sterility—Its Cause and Its Treatment. By J. Jay Rommer, M.D. Price, $12.50. Pp. 427, with 259 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1952.

Here is an extremely thorough study of human sterility and its many problems. The study includes a brief discussion of pertinent anatomy, embryology, and physiology involved in coitus and fertilization, including original work on uterine activity during coitus. A generous outline of gynecological pathology is presented, with an explanation of its relationshp to sterility. A lengthy treatment of the little known, and generally overlooked, factors concerned with sterility makes all the "trimmings" available to the reader. Procedures, including those for both office and hospital, which may be necessary for a complete evaluation of a sterility problem are described in detail. Treatment of the pathological conditions uncovered is discussed at length, including much on the psychic phase of such problems. Artificial insemination is discussed. Throughout this book is a generous number of tables, graphs, and photos.

Many controversial subjects are included in the text. Some of the ideas are not generally accepted. The organization of the material includes some overlapping and repetition of subject matter. On the whole, however, this book offers an all-inclusive, illustrated study of sterility in the human male and female.

Injury of the Xiphoid. By Michael Burman, M.D. ,and Samuel E. Sinberg, M.D. Price, $3.50. Pp. 92 with illustrations. Columbia University Press, 2960 Broadway, New York 27, 1952.

This is a fascinating little monograph on medical and surgical conditions of the xiphoid process. It is well written and beautifully printed and illustrated.

Transaction of the Thirteenth Conference on the Problems of Aging. By many contributors; edited by Nathan W. Shock. Price, $4.00. Pp. 194, with illustrations. Josiah Macy, Jr. Foundation, 565 Park Ave., New York, 1951.

This volume of the Macy Foundation Conferences on the Problems of Aging is the product of an attempt at a multidiscipline approach to an important subject. Participants in the discussion included pathologists, biochemists, biologists, sociologists, clinicians, anthropologists, endocrinologists, public health experts, and a librarian "concerned with Leonardo da Vinci's studies of the aging process."

The discussion ranged from methods of measuring physiological age to the proper use of leisure time and the need for suitable housing for the aged. The presence of experts from England, Denmark, and Switzerland added much to the interest of this Symposium.

Anyone with a social conscience or with an awareness of the approach of old age will find this volume a very stimulating contribution.

Functional Endocrinology from Birth Through Adolescence. By Nathan B. Talbot, M.D.; Edna H. Sobel, M.D.; Janet W. McArthur, M.D., and John D. Crawford, M.D. Price, $10.00. Pp. 638, with illustrations. Harvard University Press, Cambridge 38, Mass., 1952.

This book on functional endocrinology is a welcome addition to the small collection of reliable textbooks on endocrinology available to medical students and physicians. It has been written by a team of clinical endocrinologists, some of them comparatively young but nonetheless keen, who have carefully set down their own experiences in a pediatric clinic. A chapter is allotted to each endocrine gland. The subject matter for each is broken down into "Basic Considerations" and "Clinical Considerations." The "basic" section will hardly satisfy the physiologist. The authors have, however, made a commendable attempt to interpret clinical findings in terms of human physiology. The book is abundantly illustrated with pictures, tables, and elaborate diagrams. The lack of an introductory chapter is a serious defect.

The special interests of the authors have claimed a disproportionately large share of the space. For instance, as many pages are devoted to the adrenal cortex as to the anterior pituitary, thyroid, and pancreatic islets combined. The well-established central position of the pituitary gland is poorly emphasized. The value of the book would have been much enhanced if this structure had not been relegated to the same status as the other endocrine glands. Only for the thyroid and testes are even brief sections devoted to relationships to the pituitary. The authors state that "supreme control [of the anterior pituitary] resides in the hypothalamus of the central nervous system." That some control exists cannot be disputed, but the authors would do well to outline their evidence for a supreme control.

Certain factual statements are out of date, e. g., "pure crystalline insulin" has a potency more nearly 28 to 30 I.U. per milligram than 22 I.U. per milligram, which was the potency assigned to the International Standard in 1935. The statement that insulin is "the most important endocrine hormone" is surely open to doubt. It is surprising to find the lactogenic hormone of the anterior pituitary mentioned only three times in isolated sentences in the book and omitted from several diagrams where it should appear for completeness.

This book will, to a considerable degree, fulfill its stated purpose of providing "for practitioners, students and investigators of medicine and surgery . . . the practical information concerning the actions of endocrine systems in health and disease, and the management of endocrinopathies in the young," but, like the other textbooks on endocrinology which have preceded it, it is not completely adequate.

Dramamine® in Vertigo

The remarkable relief afforded by Dramamine in motion sickness has led to studies of its possible value in allied conditions.

Dramamine apparently depresses hyperstimulation of the vestibular apparatus. Thus it is an effective means of relieving the nausea and vertigo which characterize dysfunctions of the middle ear.

Accepted Uses for Dramamine
(BRAND OF DIMENHYDRINATE)

MOTION SICKNESS

NAUSEA and VOMITING associated with
- pregnancy
- drugs (certain antibiotics, etc.)
- electroshock therapy
- narcotization

VESTIBULAR DYSFUNCTION associated with
- streptomycin therapy

VERTIGO in
- Ménière's syndrome
- hypertensive disease
- fenestration procedures
- labyrinthitis
- radiation sickness

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

SEARLE *Research in the Service of Medicine*

"...failure, according to some of the newer evidence...touches off at once a mechanism that hungrily promotes the tubular reabsorption of sodium, just the sort of thing that the mercurials combat so well."*

...and none better than

MERCUHYDRIN®

intramuscularly

subcutaneously or

intravenously

*Beckman, H.: Pharmacology in Clinical Practice. Philadelphia, W. B. Saunders Company, 1952, p. 172.

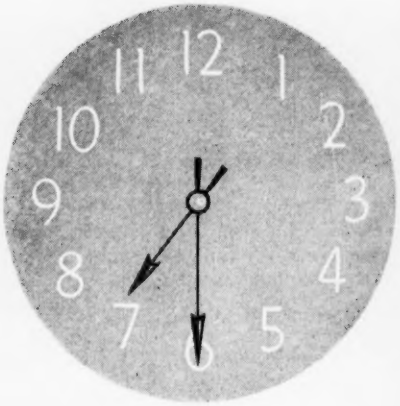
MERCUHYDRIN

(brand of meralluride, U.S.P.) *sodium*

Ampuls of 1 cc. and 2 cc. and 10-cc. vials

Leadership in diuretic research

Lakeside LABORATORIES, INC., MILWAUKEE 1, WISCONSIN



habit time

- Habit Time of Bowel Movement—not merely relief of constipation—is secured by proper use of Petrogalar.

Petrogalar promotes development of normally hydrated, comfortable and easily passed stools.

Once achieved, the normal bowel habit may often maintain itself even though the dosage of this adjuvant is slowly tapered off.

PETROGALAR®

AQUEOUS SUSPENSION OF MINERAL OIL, PLAIN

Supplied: Bottles of one pint

Wyeth®

Azulfidine

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

Brand of Salicylazosulfapyridine

a new drug for the treatment of ulcerative colitis.

Azulfidine has been clinically tried for several years at leading Swedish and American hospitals with very good results, and is considered a "drug of choice" by [1] American specialists in the treatment of ulcerative colitis.

The effect of Azulfidine is sometimes very rapid, and the diarrhea may cease after 2 or 3 days of treatment. The drug should, however, in all cases be given in courses of two weeks on and one week off, until all symptoms have disappeared.

Literature sent on request.

Azulfidine is supplied in bottles of 100, 500 and 1000 tablets.

1. Bargen: Chronic Ulcerative Colitis. Charles C Thomas, Publisher. 1951. Springfield, Illinois.

Pharmacia Laboratories, Inc.

Executive Offices: 270 Park Avenue, New York 17, N. Y.

Sales Offices: 300 First Street, N. E., Rochester, Minn.

RECORD FORMS FOR EVERY PRACTICE

- ANNOUNCEMENTS
- BOOKKEEPING SYSTEMS
- PATIENTS' RECORDS
- LETTERHEADS
- ENVELOPES
- PROFESSIONAL CARDS
- FILES AND SUPPLIES

America's Largest Printers to the Professions

HISTACOUNT®

ACTUAL SAMPLES CATALOGUE SENT ON REQUEST

For 25 years, the trade mark *HISTACOUNT®* has symbolized America's largest printer catering exclusively to the Medical profession. *HISTACOUNT®* stands for highest quality at low prices, with an unconditional money-back guarantee on every item.

PROFESSIONAL PRINTING COMPANY, INC.
202-208 TILLARY STREET BROOKLYN 1, N. Y.

Gentlemen: Send literature and samples of "Histacount" Record Forms.

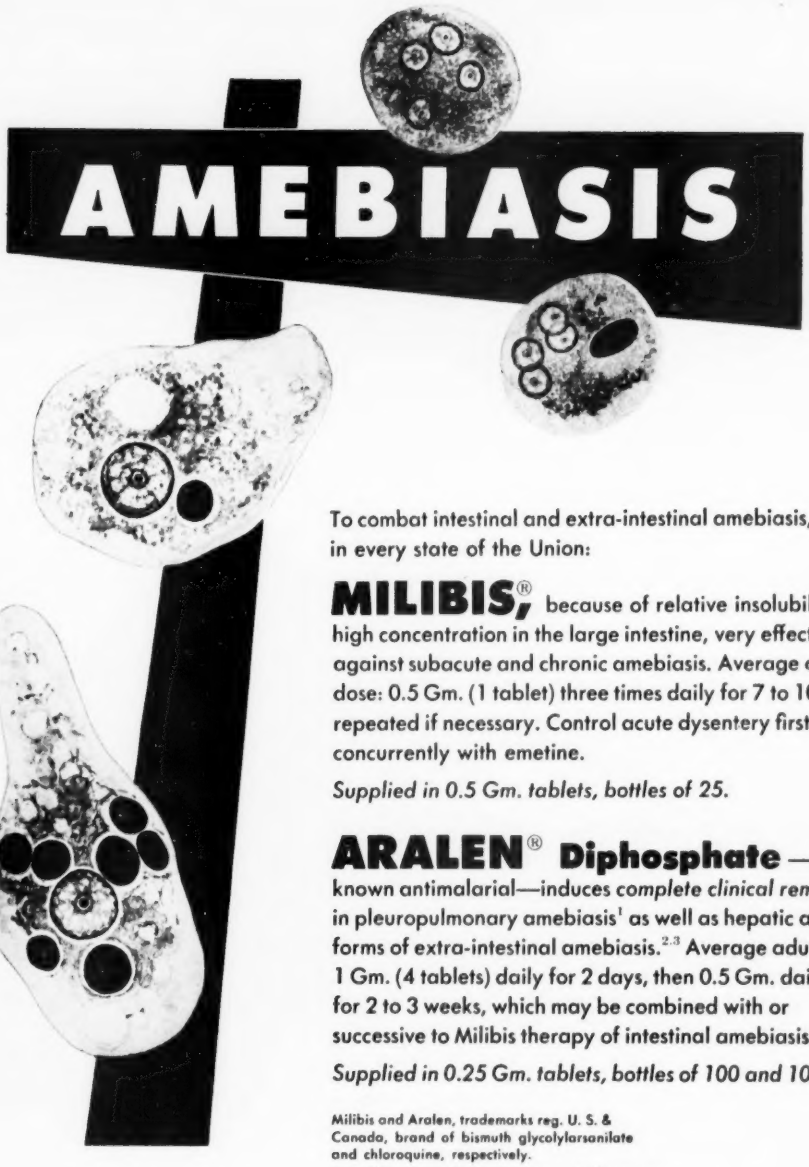
My specialty is: _____

Also send literature on the items that are checked at right...

- ☐ Stationery Products
- ☐ Bookkeeping Systems
- ☐ Files & Filing Supplies

ATTACH THIS COUPON TO YOUR LETTERHEAD OR RX BLANK H-2-3

EVERYTHING FOR YOUR OFFICE WITHOUT LEAVING YOUR DESK



To combat intestinal and extra-intestinal amebiasis, found in every state of the Union:

MILIBIS,® because of relative insolubility, assures high concentration in the large intestine, very effective against subacute and chronic amebiasis. Average adult dose: 0.5 Gm. (1 tablet) three times daily for 7 to 10 days, repeated if necessary. Control acute dysentery first or concurrently with emetine.

Supplied in 0.5 Gm. tablets, bottles of 25.

ARALEN® Diphosphate —the well known antimalarial—induces *complete clinical remission* in pleuropulmonary amebiasis[1] as well as hepatic and other forms of extra-intestinal amebiasis.[2,3] Average adult dose: 1 Gm. (4 tablets) daily for 2 days, then 0.5 Gm. daily for 2 to 3 weeks, which may be combined with or successive to Milibis therapy of intestinal amebiasis.

Supplied in 0.25 Gm. tablets, bottles of 100 and 1000.

Milibis and Aralen, trademarks reg. U. S. & Canada, brand of bismuth glycolylarsanilate and chloroquine, respectively.

1. Lindsay, A. E., Gossard, W. H., and Chapman, J. S.: *Dis. Chest*, 20:533, Nov., 1951.
2. Conan, N. J., Jr.: *Am. Jour. Med.*, 6:309, Mar., 1949.
3. Emmett, J.: *J.A.M.A.*, 141:22, Sept. 3, 1949.

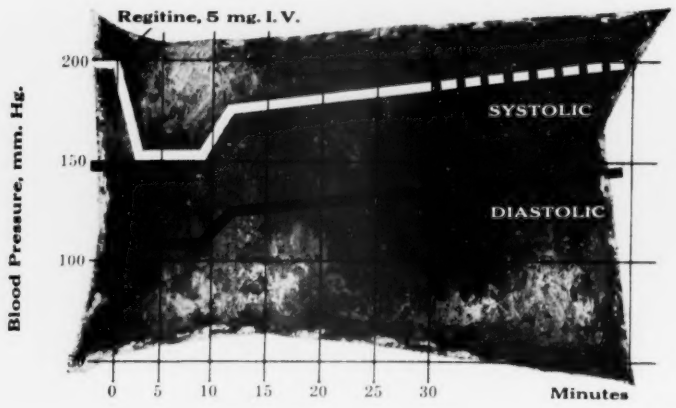
Illustrated brochure on request.

WINTHROP-STEARNS INC.
New York 18, N. Y. Windsor, Ont.

PHEOCHROMOCYTOMA

causes

one curable form of hypertension



Regitine®

the preferred diagnostic agent

Because of its specificity, this potent adrenergic blocking agent affords an eminently safe, accurate, and simple test for the diagnosis of the hypertension-producing tumor – pheochromocytoma.

When it is left untreated, pheochromocytoma is a progressive and eventually fatal condition. After diagnosis, surgical removal of the tumor effects a complete cure. Therefore, "careful consideration of the possible presence of a pheochromocytoma in every patient with hypertension must now be regarded as a diagnostic obligation."[1] Testing is quickly and simply done with Regitine.

The above chart is a schematic representation of the type of response that you can anticipate in the adult hypertensive patient who does have a pheochromocytoma.

For complete information contact your Ciba Professional Service Representative or write to the Medical Service Division.

REGITINE methanesulfonate (phentolamine methanesulfonate Ciba)
REGITINE hydrochloride (phentolamine hydrochloride Ciba)

1. DECOURCY, J. L. AM. J. SURG. — IN PRESS

Ciba Pharmaceutical Products, Inc., Summit, New Jersey

2 / 1962-M